HARMONY BIOSCIENCES (NASDAQ: HRMY)

The Latest Price-Gouging Ploy By The Grifter Who Inspired Convicted Felon Martin Shkreli, But This Time People Have Blood On Their Hands: A $175,000 Per Year Drug With Alarming Toxicity And A Trail Of Covered-Up Deaths And Injuries; No Efficacy; A Non-Existent Mechanism Of Action; Sham Patents; Based On Scam Clinical Trials In Places Like Russia And Turkey By A French Quack; Pushed Via False Advertising And A Vast Off-Label And Physician Kickback Scheme

We are shortly filing a Citizen’s Petition with the FDA requesting withdrawal of approval of Wakix. If you have experienced or are aware of serious adverse events, particularly those involving emergency care, hospitalization, or death, such as cardiac events, seizures, fainting, dizziness, blurred vision, anaphylaxis, liver or kidney abnormality, spontaneous abortion, psychiatric issues, or withdrawal symptoms, please email us at contact@scorpioncapital.com or anonymously via the contact form on our site.

- One of the most thoroughly corrupt healthcare schemes in recent years, deserving of criminal and political scrutiny, given the recent Aduhelm debacle and Congressional outrage at previous ploys by Harmony founder Jeff Aronin.
- Harmony’s drug Wakix (pitolisant) is a repeat of the Seldane (terfenadine) saga, another histamine antagonist that the FDA pulled from the market and which is the poster child for cardiac toxicity via fatal QT prolongation/arrhythmia. Wakix is worse.
- We obtained dozens of serious adverse event reports from the FDA via Freedom of Information Act requests filed over several months, and they paint a devastating picture of the drug’s risk to even young, otherwise healthy patients, including a recent sudden cardiac death, 2 weeks after starting Wakix on the day it was titrated to the highest dose.
- A physician alerted us to a recent, unreported adverse event where a healthy 42 year-old was rushed to an emergency room and hospitalized shortly after initiating Wakix, due to what the physician indicated was drug-induced arrhythmia.
- We detail 12 deaths in the foreign clinical trials, all in the drug arm, none in placebo, despite exclusion criteria for cardiac risk.
- We believe explosive information was concealed from the FDA that would have prevented approval in 2019 – provided to us by an individual involved with the “successful” key trial, who stated it was prematurely, quietly halted due to liver toxicity.
- Scientists involved with identical H₃ antagonist/inverse agonist programs at three of the world’s largest pharma companies provided us with detailed information and data corroborating pitolisant’s toxicity and other fatal flaws, based on their independent synthesis and analysis of the molecule as part of their terminated efforts to develop a similar drug.
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“The people prescribing Wakix are the dumb doctors or they’re speakers for the company, not the ones I would want my family seeing for narcolepsy...the speakers are prescribing like crazy, and I'm like, okay, how are you finding the patients?...If Wakix was going to be a hit, it would have been a hit by now...I scratch my head wondering why patients that are on it are on it.”

Physician and professor at Stanford with a large narcolepsy practice; the pre-eminent sleep center in the US, which many in the field look to for thought leadership

“Bro. These guys invented price increases. I literally learned it from them.”

Martin Shkreli, speaking of Harmony founder and chairman Jeff Aronin’s previous company Marathon Pharmaceuticals

“I put a lot of money on the fact that dude, I'm probably their number-one guy. I can't imagine somebody more aggressive than I am about this...we probably went balls to the wall to get people on it...100% of every narcoleptic is offered Wakix, absolutely...we are extremely aggressive about offering Wakix...who the hell wouldn't want to write this shit?”

An Alabama physician and recipient of what we believe to be kickbacks via Harmony’s “Speakers Program,” who told us he has >100 patients on Wakix – a number that vastly exceeds the number of statistically-probable narcolepsy patients in his practice radius, and who we think drives ~5% of Harmony’s revenue and shows its dependence on a few corrupt high-volume prescribers
“I'm surprised there hasn't been regulatory pressure put on them. I'm surprised…listen, I've worked for a lot of pharma companies, okay? And I've never seen the goofiness that I've seen with this company…the pressure to produce…it was just terrible. It was awful. A lot of pressure on sales, a lot of pressure on getting referrals…it was just a lot of pressure…I mean, how many cataplexy patients are there? Oh my god. How many are there? Get in no matter how you need to get in; get the referrals…I mean, as far as entertaining and speaker's programs, like these guys do - I've never seen it.”

-Ex-field reimbursement manager working with Harmony, who stated most of his team and a large number of sales reps resigned due to pressure to support improper conduct.
“The overwhelming sense in the company is they are fudging the numbers...no sales consultant has any transparency or visibility into how many patients are on drug in their territory. I have never seen that before in a pharma company...My sense, is absolutely...the bottom of this will fall out. They're going to get found out or payors are going to bolt... the discontinuation rates, investors are going to squeeze them for how many patients are you treating? How many patients are on drug? So, that's going to come out, and I think that could be alarming.”

-Ex-Harmony territory manager for a large region in the northeast
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Executive summary

Part 1. Pitolisant’s troubled history: an old, failed compound no reputable pharma company would touch; an inherently dangerous molecule in a class plagued by safety problems and recalls.

Introduction to the real Harmony Biosciences.
Harmony Biosciences is a house of cards, built on an extensive scientific, clinical, and commercial fraud designed to exploit every weak link in the US healthcare system. A revolving door of CEO's, CFO's, and bad actors, the last CEO’s surprise departure on Jan 6th signals the end is near, as doctors and patients sour; territories struggle; and fake metrics cover up a looming collapse. Our conclusions are based on a 4-month investigation that included ~50 research interviews, including 14 ex-employees and executives; 16 physicians, including Harmony’s highest volume prescribers and speakers; 5 trial investigators, including key figures in pitolisant’s trials and papers; and 4 senior scientists involved in failed H3 programs at large pharma companies, including one who published the foundational research. In addition, we engaged a pharmacology consultant who has conducted hundreds of pharmacokinetic studies, on a months-long review of pitolisant's data and FDA package, as well as specialized experts such as a leading figure in hERG/drug-induced cardiotoxicity.

A dangerous molecule in a drug class plagued by toxicity and FDA recalls
Histamine receptor antagonists like pitolisant have a uniquely risky molecular structure with a long history of cardiotoxicity and FDA recalls, due to hERG channel blockade and the potential to cause sudden death via QT prolongation and arrhythmia. Of nine drugs withdrawn by the FDA for cardiotoxicity, two were in this class and the rest share binding and other similarities with pitolisant. The drug chemistry literature is unequivocally clear on the danger, which stems from the similarity between the pharmacophore of the histamine receptor and the hERG channel. Ominously, numerous studies indicate that within the histamine class, the H3 receptor sub-class – of which pitolisant is the first and only approved drug – is particularly cardiotoxic, as its structure contains a piperidine ring and other features that are the top predictor of hERG liability in drug screens.

Pitolisant’s origin: an old, failed compound no reputable drug company would touch
Pitolisant was first synthesized a quarter-century ago, with a long and twisted history of failure - so old that we unearthed a 2002 paper that shows its structure under a different name, creating prior art that would instantly invalidate its sham patents if we filed an Inter Partes Review. Using the Jeff Aronin playbook of licensing an old, toxic drug with foreign clinical trials and re-packaging it as a high-priced rare-drug in the US, Harmony licensed it from its developer, a small French lab with a poor reputation, called Bioprojet and run by an idiosyncratic scientist named Jean-Charles Schwartz. The timeline of pitolisant papers and trials is troubling, suggesting that Bioprojet was well aware of its myriad dangers and flaws and rejected it as their lead H3 candidate multiple times over a decade.
Executive summary (cont’d)

Part 1. Pitolisant’s troubled history (cont’d)

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The elephant in the room: how did a small, troubled French lab miraculously “succeed,” when histamine H3 receptor antagonists/inverse agonists have a 40-year history of well-documented failure and toxicity. Our research indicates that virtually every global pharma company had an active H3 ligand development effort that was terminated. We summarize the programs and detail the reasons for their failure – and why they render Harmony’s claims implausible.

Other pharma companies tested pitolisant and their color is damning 78-103
We uncovered buried evidence that a number of major pharma companies synthesized pitolisant as a comparator and concluded that it suffers from cardiotoxicity and other fatal flaws. We first found papers establishing that Bioprojet’s claims were not reproducible, and then spoke with three senior scientists from Abbott, Johnson & Johnson, and GSK, who played key roles in their respective, terminated H3 programs and provided detailed information. The color was damaging, as it suggested that large players looked at licensing pitolisant 10-15 years ago and ran for the hills – “There’s a piece of information. I know more than I’m telling you…I knew they had cardiovascular issues…that compound had issues…the main issue is it had a cardiovascular signal…I’m sure it was known as soon as people profiled it.” The scientists shared troubling anecdotes about Bioprojet – “mediocre reputation” - and Schwartz’s conduct, such as his allegedly shouting from the audience at presenters at conferences: “It was bizarre. I’d never come across that before”; “getting into screaming matches”; “he did it to somebody from Novo Nordisk”; “he attacked a guy from GSK…it’s just insane.”

Part 2. Clinical evidence of pitolisant’s toxicity is overwhelming, with sham safety studies that misled the FDA into committing grave errors during its review.
Adverse event reports indicate an unfolding tragedy.

The early warning signs in Bioprojet’s pitolisant clinical development program 104-116
The first pitolisant patient data was published in 2007 and indicates two danger signals: 1) plasma levels of the drug were highly elevated - a stark contrast to later claims which conceal the risk, given the dose-dependent relationship with hERG/QT prolongation; 2) the adverse event data indicated symptoms consistent with QT prolongation as well as an attempt to conceal it. In addition, although the narcolepsy trials tellingly fail to ever show cardiovascular data, we uncovered troubling QT data in two trials for a different indication, including a fatality (HAROSA 1 and HAROSA 2). Neither trial appears to have been evaluated by the FDA or EMA as part of their approvals.
Executive summary (cont’d)

Part 2. Clinical evidence of pitolisant’s toxicity is overwhelming (cont’d)

A PK failure that never should have made it past phase 1 – underestimated plasma levels are key driver of risk

We believe Harmony and Bioprojet have engaged in a systematic effort to conceal and under-estimate pitolisant’s plasma levels, which the evidence indicates are substantially higher and more variable than claimed. Pitolisant’s purported safety profile hinges on plasma levels not exceeding certain thresholds, as evident in the dose and titration guidelines on the label which exhibit concern of adverse effects. The max dose is 35.6 mg/day, but half that in patients with hepatic or renal impairment or who are poor metabolizers of CYP2D6.

Cardiac safety data submitted to the FDA was a sham, and the agency’s interpretation exhibits grave errors

The QT/cardiac safety studies submitted to the FDA are misleading and grossly understate the risk of QT prolongation and cardiovascular danger. The FDA’s interpretation of Harmony’s QT data was deeply flawed. We engaged two consultants to analyze, reverse-engineer, and correct the cardiac safety data - a pharmacology specialist, and a leading figure in drug-induced cardiotoxicity. They characterized the FDA submissions as “intentionally misleading” and “sneaky,” and strongly disputed the agency’s assessment, as the drug has no cardiac safety margin as the FDA inferred, and can easily spike to red alert level.

CYP2D6 liability and drug-drug interactions amplify toxicity; the FDA’s assessment was based on misleading data

Pitolisant is plagued by a potent CYP2D6 liability and extensive drug-drug interactions, which can exponentially multiply the risk of QT prolongation as well as adverse effects related to liver, kidney, or other toxicity. The FDA’s assessment of CYP2D6 safety issues and resulting dosage adjustments are based on highly misleading data from Harmony, which we believe flagrantly misrepresents the potential for elevated plasma levels of pitolisant and the associated cardiovascular hazard.

Thirteen deaths during the pitolisant development program; case narratives are consistent with known toxicity

The occurrence of 13 deaths during trials, in the pre-approval period – 12 in the foreign trials and one in the US EAP program - was a canary in the coal mine that predicted the post-marketing safety debacle: The deaths are striking for two reasons. First, 100% of the fatalities were in patients on the drug and none on placebo. Second, they occurred despite the trials cherry-picking less vulnerable patients via exclusion criteria for cardiovascular, hepatic, or renal disorders. The FDA exhibited skittishness but gave Harmony the benefit of the doubt, taking a wait-and-see attitude that we expect will now be less permissive: “The postmarketing data should also be monitored for sudden deaths and cardiovascular and respiratory adverse reactions.”
Executive summary (cont’d)

Part 2. Clinical evidence of pitolisant’s toxicity is overwhelming (cont’d)

FDA’s sensitivity to potential CNS and hepatic safety signal will now be highly problematic for Harmony

In addition to cardiotoxicity, the FDA’s review exhibited skittishness at CNS and hepatic issues, which we expect to be perilous given the flood of such adverse events post-approval, and in particular certain case narratives we obtained by FOIA. The agency indicated a keen interest in the post-marketing safety data for seizures and convulsions, which it found “notable” and “of special interest” during its review. The agency also noted a worrisome signal in a pitolisant phase 1 PK study for Prader-Willi Syndrome, where one of eight pediatric patients “experienced hepatic enzyme elevation.”

Hypereosinophilic syndrome and drug-induced phospholipidosis overlooked by FDA

Pitolisant exhibits a clear and startling signal for hypereosinophilic syndrome, which we found buried in a single line the EMA pitolisant review and was never assessed by the FDA – and which we think Bioprojet has covered up. The syndrome is often “associated with eosinophilic infiltration of tissues that can potentially lead to irreversible, life-threatening organ damage.” We could locate no mention of hypereosinophilia in any pitolisant papers or trials. As we studied the 13 deaths during pitolisant development program, a large percentage presented cardiopulmonary symptoms remarkably consistent with the syndrome. Harmony is also silent on phospholipidosis, highlighted in the H3 literature as a toxicity inherent to the class. Pharma companies who synthesized pitolisant as a comparator noted its “potential for phospholipidosis” as one of many “important hurdles for this novel compound.”

FAERS database confirms a massive toxicity issue since pitolisant’s approval in 2019, including a recent fatality

The FDA Adverse Events Reporting System (FAERS) indicates a clear safety problem, with 612 case reports for Wakix through Dec 31, 2022, almost all from 2019 to 2022, despite the relatively small number of patients who have taken the drug. We think lags in the database and/or reporting games by Harmony mean the number of actual case reports in the last two years is several-fold higher. We note 64 respiratory/thoracic and 26 cardiac reports. 137 of the 612 cases are classified as serious adverse events, with a large number that involve cardiac arrest, myocardial infarction, loss of consciousness, QT prolongation, atrial fibrillation, myocarditis, palpitations, vertigo, hypertension, and stroke. with a recent fatality that presents as QT-related. We count 42 hospitalizations., and 29 that mention dizziness, which along with seizures is one of the top symptoms of QT prolongation.
Executive summary (cont’d)

Part 2. Clinical evidence of pitolisant’s toxicity is overwhelming (cont’d)

Individual case narratives for serious adverse events are devastating, obtained via FDA FOIA requests

We obtained dozens of serious adverse event reports from the FDA via Freedom of Information Act requests filed over several months, and they paint a devastating picture of the risk the drug poses to even young, otherwise healthy patients. Most case narratives contain incomplete information or are too heavily redacted to interpret, but we present 22 with a sufficient fact pattern to be troubling. Four of the narratives suggest attempts by the physician and/or company representative to cover up the event.

Unreported case of drug-induced arrhythmia and hospitalization is a striking signal, given n=16 doctor interviews

We interviewed 16 prescribers, and one provided a detailed narrative of a healthy 42-year old patient who was taken to an ER and hospitalized for drug-induced QT prolongation and arrhythmia, 8 weeks after starting Wakix. To easily find such a case in a small sample of doctor calls is troubling, and makes one wonder how many other cases are out there. The doctor had 10 patients on Wakix; all but 2 discontinued after he alerted them. He stated that he conveyed the information to his Harmony rep, who expressed concern as the patient had no history and didn’t meet any warnings on the label – we found no report in the FDA FAERS database, leading us to wonder if Harmony buried it. We note key features of the case: no prior medical history or other medication beyond an anti-hypertensive for mild hypertension - “pretty healthy guy”; a conscientious prescriber who did full panels prior - “nothing, no red flags”; patient was at dinner and became diaphoretic, somnolent, and was “going to pass out”; patient’s wife was a nurse who recognized the symptoms and acted quickly, averting potential disaster; cardiologist who admitted patient diagnosed it as drug-induced arrhythmia.

Ominously for Harmony, we note a page on the FDA’s site: “One individual report can make a difference. Many drug withdrawals began with one clinical report that initiated further investigation…a single report ultimately led to the removal of terfenadine from the market. This report potentially saved many lives and led to a better understanding of the mechanism involved in causing torsades de pointes. Almost all drugs are now evaluated prior to being released on the market for their potential to induce cardiac arrhythmias, also as a result of this single case report.”
Executive summary (cont’d)

Part 3. The foreign clinical trials that led to FDA approval were a scam, a poster child for the loopholes and abuses in the expedited approval pathway, reminiscent of the recent Aduhelm controversy.

The foreign clinical trials that led to FDA approval lack credibility
The trials are a poster child for the weaknesses and loopholes in the FDA’s fast-track approval process, where it appears that anything suffices for evidence in the case of a rare condition. Our interviews with the Harmony executives and medical advisers indicate that even they were concerned about Bioprojet’s data and were “lucky” to get FDA approval. The trials are little more than blatant, dishonest attempts to manipulate study design to achieve a predetermined outcome, making a mockery of the scientific method and highlighting abuses by companies like Harmony and their consultants as they game the extraordinary deference the FDA grants applicants under its accelerated approval pathways. In particular, Harmony’s clinical trials indicate a pattern of cherry-picking “successful” trials and burying the ones that undermine the drug. The FDA’s failure to incorporate the failed trials into its review was an error, particularly as they were the most relevant and telling.

Part 4. The most devastating physician commentary we have ever heard, even from Harmony’s speakers, medical advisors, and highest volume prescribers, based on 16 in-depth interviews.

Physician interviews indicate a failed launch; an ineffective product with high discontinuation rates, and no more growth
We conducted interviews with 16 current and former prescribers of Wakix, and they painted the most damning and bearish picture of a drug we have ever seen. We consulted a broad, geographically diverse panel across various practice settings, and specifically sought a number of Harmony’s speakers and highest volume prescribers – we spoke with 6 of the top 10 recipients of payments from Harmony per the CMS OpenPayments database. We summarize the main findings: there are almost no high volume prescribers except paid speakers; supernormal patient discontinuation rate of 30-100%; most physicians, even speakers, don’t think Wakix has any effect; essentially every doctor, including speakers, only prescribes it as a 3rd or 4th line drug in a cocktail; failed launch with no buzz or enthusiasm among sleep physicians; Harmony’s small market opportunity is saturated, with usage peaking in 2022 and no growth remaining in terms of new patients or prescribers; new patient starts have plummeted, especially in the last 6 months; and that Wakix competes in a crowded field with other drugs like sodium oxybate that work better.
Executive summary (cont’d)

Part 4. The most devastating physician commentary we have ever heard (cont’d)

Wakix’s only selling point – that it’s not a controlled substance – was dismissed by physicians as irrelevant. Harmony’s sales and marketing for Wakix have one and only angle – that it is easier to prescribe because it’s not a controlled substance. Given that Wakix is inferior to cheap generics like modafinil and physicians at best use it as a third or fourth line drug in cocktail, it has no other reason to exist. Unfortunately for Harmony, every single physician we interviewed indicated there is no value proposition to Wakix being non-controlled: 1) prescribers are already registered to write controlled substances; 2) they have to write periodic refills for Wakix patients anyway as it’s a third or fourth line drug that is almost never used as a monotherapy, and the other drugs in the cocktail are controlled substances; and 3) Wakix’s centralized pharmacy is far more onerous to deal with than controlled drugs. We quote numerous doctors who indicate that Harmony leads with and pushes the “non-controlled substance” message, but they repeated the same refrain: “absolutely no benefit from it”; “it doesn’t matter”; “I don’t know what the big deal is”; “what kind of value is there? I don’t see it.”

Part 5. A non-existent mechanism of action – a pharmacokinetic disaster, falsely advertised as increasing histamine levels in the “human brain,” with no association between histamine and sleep disorders.

Mechanism of action – “increases histamine levels in the human brain” – is unproven and hence false advertising. Harmony markets Wakix to patients and doctors as a “first-of-its-kind medication that increases histamine levels in the human brain” – the critical claim upon which the entire premise and purported mechanism of action rests. However, neither Harmony nor Bioprojet has ever shown this to be the case, which renders their advertising and marketing false, in our opinion. The claim is repeated throughout Harmony’s consumer marketing website, yet we can only find citations at the bottom of one page – and none of those papers say anything of the sort.

Even if Wakix increased histamine levels, Bioprojet admits it has no correlation with narcolepsy or sleepiness. Bioprojet once published a telling paper that discredits any link between histamine levels and hypersomnia conditions such as narcolepsy, cataplexy, or sleepiness. Thus, even if there was evidence that pitolisant increases histamine levels in the brain, it wouldn’t matter as their own research unequivocally undermines the purported mechanism of action. The conclusions are devastating, as they showed no association with any current or contemplated indication, such as sleepiness whether EDS or idiopathic hypersomnia, whether measured objectively via sleep tests or subjectively via ESS.
Executive summary (cont’d)

Part 5. A non-existent mechanism of action (cont’d)

Pitolisant’s pharmacokinetic profile is a disaster – bioavailability problems and blood-brain penetration

A more fundamental issue is its pharmacokinetic profile. First, a lack of bioavailability, which refers to the percentage of active drug that gets into the blood, without which an insufficient amount is available for a therapeutic effect. Pitolisant is subject to extensive first-pass metabolism by CYP3A4, which means most of the drug is lost by metabolism in the liver and gut before it gets into general circulation, thereby preventing enough of it from getting to the target organ, i.e., the brain. Second, the compound has problems with CNS uptake and blood-brain penetration. We hired a pharmacology consultant to review Harmony’s PK claims, and the analysis leads us conclude they are riddled with red flags, discrepancies, contradictions, and omissions to the point that we find them suggestive of fraud and an intent to mislead the FDA. As a third red flag, the time to maximal effect on the EDS endpoint (excessive daytime sleepiness) further undermines pitolisant’s supposed mechanism of action.

Part 6. A commercial fraud where the end is near, as a failed launch propped up by off-label prescribing and kickbacks runs out of tricks, with sales territories in trouble as new patients and prescribers vanish, per interviews with 14 ex-employees including 8 territory managers.

Harmony’s sales are dependent on a handful of physicians, paid via a speakers program that ex-employees described as a blatant kickback scheme; one of Harmony’s top speakers estimated that he and four others he knows are responsible for 5-700 of all Wakix patients - 20-30% of total revenue depending on how one does the math. Ex-employees consistently describe Harmony’s sales and business model as being dependent on a small number of high-volume prescribers – “whales” who are typically paid promotional speakers, which the ex-employees described as a quid pro quo and inducement for doctors willing to write large numbers of prescriptions. We interviewed 14 former Harmony employees, a majority of whom were sales/territory managers in large regions across the country, who described dangling the speakers program as an inducement or threatening to remove doctors form the program if they didn’t write enough prescriptions. Speaker’s programs which constitute kickbacks or rewards are flagrantly illegal, resulting in high-profile indictments at companies like Insys, for example, where the CEO, physicians, and others were sentenced to prison. Fraudulent speakers programs are the target of heightened scrutiny, as evidenced by a 2020 “Special Fraud Alert: Speaker Programs” issued by the HHS Office of Inspector General. Harmony’s program is a textbook case of the red flags listed in the memo.
Executive summary (cont’d)

Part 6. A commercial fraud where the end is near (cont’d)

**Off-label prescribing scheme allegedly drives 40% or more of Harmony’s prescriptions**

Given the small number of narcoleptics and even smaller number of those with cataplexy, former employees allege that Harmony is dependent upon an off-label marketing strategy that illegally promotes Wakix for 1) excessive daytime sleepiness even if there is no narcolepsy; and 2) incentivizes territory managers (via a highly unusual comp plan) and high-volume prescribers (via the speaker’s program) to falsely indicate cataplexy symptoms even if none are present, in addition to misrepresenting that reimbursement requirements have been met. One ex-territory manager explained it as a textbook off-label scheme: “the trick was to get it covered under cataplexy…now, we market it for – I don’t know what we said…." He described a wink-wink game where reps coach or cajole the doctor to indicate cataplexy by “really stretching it…so, you get into games like that…." An ex-field reimbursement manager estimated 40% of prescriptions are off-label; alleged that it was Harmony’s strategy since inception; and that numerous reimbursement and sales staff resigned due to pressure to support improper conduct.

**A small, saturated market with a looming sales collapse, as sales reps struggle and run out new patients and prescribers**

We interviewed 14 ex-Harmony employees, a majority of whom were territory sales managers. A significant number left relatively recently and indicated they receive general market color from former colleagues. They universally painted a picture of a tiny market that Harmony quickly saturated, with the trend hitting a wall 2 years after the 2019 launch. They indicate the sales difficulties worsened in mid-2022 and accelerated recently, as regions ran out of potential patients or doctors failed to see clinical efficacy, and that large numbers of previously successful reps have been placed on PIP’s – Performance Improvement Plans – as they miss quotas. One ex-sales manager stated that “morale amongst the salesforce is really low…it’s not a happy environment…it’s a pretty sour environment,” and indicated increasing management pressure: “there’s certainly more pressure…I’ve heard that they are struggling.”
John Jacobs abruptly fled as Harmony’s CEO on January 6th, throwing the company under a bus on the eve of the JP Morgan healthcare conference. The stock fell as investors wondered what he knew, and why he left for a mediocre comp package at a troubled vaccine maker (NVAX) with a fraction of the market cap. We had already been investigating HRMY for months, and chuckled as it reminded us of Jeff Skilling’s surprise resignation from Enron. Most now forget Skilling’s pathetic attempt to flee, a few months before a baffled market came to know what he did. Skilling, we note, still ended up in prison – an outcome as far from his mind as we presume it is for Harmony executives and the high-volume prescribers in its speaker’s program. We encourage them to study the leaderboard of Insys prosecutions, a close analogy to Harmony’s business model vis-a-vis the False Claims Act, Anti-Kickback Statute, and other laws.

Founder and Former Chairman of the Board of Insys Therapeutics Sentenced to 66 Months in Prison

Manhattan Doctor Sentenced To More Than 17 Years in Prison For Bribery And Kickback Scheme

In March 2013, a Regional Sales Manager for Insys sent an email to FREEDMAN informing him that he would receive more Speaker Programs in the coming months because Insys wanted prescriptions of Subsys to increase, and urging FREEDMAN to put more patients on Subsys. FREEDMAN responded, in part, “Got it,” and significantly increased his Subsys prescriptions in the following months, during which he received approximately $33,600 in Speaker Program fees.

With Jacobs gone, Harmony is now on its third CEO. The first, Bob Repella, pled guilty and was sentenced for paying a $120K bribe to get his daughter into college. Typical of scams, the company is a revolving door of C-level executives, several of whom we spoke to. Harmony is also on its third CFO, Sandip Kapadia, with whom we are well acquainted and whose arrival at a biotech is now one of our top indicia of fraud. We’ll get to him shortly. A CEO unexpectedly resigning from a pump-and-dump is an ultra-predictive sign that the end is imminent. They usually do so to dump their stock with haste, under the cover of night without a Form 4. Harmony has secrets, and Jacobs knows what they are. So do we. The company tells investors almost nothing, demurring on basic metrics like the price of the drug, price increases, gross vs. net, refill and discontinuation rates. The stock goes up and down based on one key metric — “average number of patients on Wakix.” For the last 8 quarters, the increase each period is 300 or 400 patients, to the penny — a curiously consistent and repetitive pattern.

Q4 2022 earnings press release, and historical figures below

Average Number of Patients on WAKIX Increased to ~4,900

<table>
<thead>
<tr>
<th></th>
<th>Q1 '21</th>
<th>Q2 '21</th>
<th>Q3 '21</th>
<th>Q4 '21</th>
<th>Q1 '22</th>
<th>Q2 '22</th>
<th>Q3 '22</th>
<th>Q4 '22</th>
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<tbody>
<tr>
<td>Average # patients on Wakix</td>
<td>2,800</td>
<td>3,200</td>
<td>3,500</td>
<td>3,800</td>
<td>3,900</td>
<td>4,300</td>
<td>4,600</td>
<td>4,900</td>
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<tr>
<td>New patient adds</td>
<td>N/A</td>
<td>400</td>
<td>300</td>
<td>300</td>
<td>100</td>
<td>400</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

Source: Harmony press release and quarterly earnings presentations
Kapadia is a supporting actor who only showed up in 2021 - Harmony is strictly Jeff Aronin’s show – but when it comes to sketchy accounting and metrics, he seems to know the role. His last job was as CFO of Intercept (ICPT), another company with a toxic drug, which we shorted successfully into its garbage NASH trial a few years ago. The stock has since imploded. We had a 1x1 meeting with him and the CEO at the JPM conference, and asked about an accounting item we thought was fraudulent. He was evasive. We asked again and he mumbled and froze like a deer, at which point the CEO terminated the 1x1 and escorted us to the door - the only time we have been kicked out of a meeting.

CFO bio per Harmony website, and articles on Interceot (ICPT), where was previously CFO
The first Harmony 10K filed under his tenure – for 2021, filed in March 2022 – contained a surprise: a “Critical Audit Matter” flagged in the auditor opinion, which refers to items that are “material to the financial statements” and involve “especially challenging, subjective, or complex judgments.” It’s flagged again in the 10K last month, concerning the **gross-to-net rebate accrual for Medicaid**. The issue is cloaked with complexity and lack of detail, but concerns a massive rebates bucket within accrued expenses - $28MM as of 12/22. It’s impact on revenue “growth” is as hard to discern as that of price increases. Harmony conceals Wakix’s price from doctors and its own sales reps. From one state’s data, we see a WAC of $136K for 2019, $155K for 2020/2021, and $175K for 2023 – a price hike of 14% in 2020/2021 and 13% in 2022. While HRMY’s 2022 revenue grew 43%, a rough estimate – the best one can do with crumbs – suggests that volume growth was far lower at ~25%.


**Critical Audit Matter in auditor opinion letter, per 10K filed last month**

**Rebate Accrual for Medicaid – Refer to “Note 3-Product Sales, Net” to the financial statements**

**Critical Audit Matter Description**

As more fully disclosed in Note 3 to the financial statements, the Company recognizes revenue on sales of WAKIX when the customer obtains control of the product, which occurs at a point in time, typically upon delivery. Product revenues are recorded at the product’s wholesale acquisition costs, net of applicable reserves for variable consideration that are offered within contracts between the Company and its customers, payors, and other indirect customers relating to the sale of WAKIX. Components of variable consideration include government and commercial contracts, commercial co-payment assistance program transactions, and distribution service fees.

The rebate provision and related liability related to the Medicaid Drug Rebate Program (the “Medicaid rebate accrual”) involves the use of significant assumptions and judgments in the Company’s calculation. These significant assumptions and judgments include consideration of legal interpretations of applicable laws and regulations, historical claims experience, payer channel mix, current contract prices, unbilled claims, claims submission time lags, and inventory levels in the distribution channel.

Given the complexity involved in determining the significant assumptions used in calculating the Medicaid rebate accrual, auditing these estimates involved especially subjective judgment.
As the sole key metric that’s disclosed, it is critical to understand what “average number of patients on Wakix” means. We can locate no methodology – over what period of time is the average calculated, what does “on Wakix” mean, and has the definition ever changed? A company simply needs to disclose patients at quarter end, and the average from period to period becomes obvious. An equally material number is the refill and discontinuation rate, which the company refuses to disclose. It is an Achilles Heel – the number of patients for a rare-drug is small, and if 50% or more discontinue within weeks or months, it’s a water bucket with a giant hole. It is self-evident that no such company can survive if patients aren’t sticky. It becomes a bottle rocket with two years of growth and a sudden collapse. The company bends over backwards to evade the question on calls, stating only that it is within the purported category average of 30-50% within 12 months.

*Jeff Dierks, Chief Commercial Officer, Aug 2022 earnings call*

And so, when you're thinking about refilling behavior, it obviously has a reflection on the average number of patients. We've talked a lot about within this category the average discontinuation rate of drugs for the narcolepsy market range between 30% and 50% at 12 months. And then again, you may have a smaller portion of discontinuation in year two and three for chronic medications, which is consistent across the industry. And although we haven’t shared specific discontinuation rate information with respect to Wakix, we’re extremely pleased with how the products being received, it falls well within that range, we continue to hear great feedback from healthcare professionals and patients.
If the 12-month discontinuation rate is 30-50%, what is it in years 2 and 3? For investors seeking a clue into Harmony’s predicament, we note HARMONY 3, a one-year foreign open-label trial, which we analyze in a later chapter. The trial followed patients for 5 years, even though the trial paper (2019) fails to disclose this fact, and nor does it show any data beyond the first year. However, an appendix buried in the EMA review for pitolisant circa 2015 contained a nugget - of 102 patients, 68 (67%) were left at 12 months, and only 44%, 37%, 33%, and 14% at years 2, 3, 4, and 5. The paper states that 90% of the patients who discontinued did so within 3 months, so the 12-month discontinuation rate of 30-50% is a 90-day figure in disguise.

**EMA review (Annex 1) indicated massive discontinuation rates.**

The open-label, long-term Phase III study (HARMONY III) assessed the long term safety of pitolisant in patients suffering from narcolepsy (with or without cataplexy) over 12 months and with an extension of up to 5 years. 102 narcoleptic patients with or without cataplexy were included in the 12 months follow-up period. 68 patients completed the first 12 months period. 45, 38, 34 and 14 patients completed the 2, 3, 4 and 5 year follow-up periods, respectively. The maximal dose received during the study was 36 mg / day in 85% of patients. After 12 months of treatment, improvements in EDS assessed by ESS score of remaining patients is of same magnitude as those observed in the other trials conducted in narcoleptic patients. The decrease in mean ESS score (SD) was -3.62 (4.63) after 1 year.

The 16 physicians we interviewed indicated that 30 to 100% of their Wakix patients discontinue, usually within weeks or a few months – hardly a surprise for a drug that doesn’t work and has side effects. We spoke with 8 former territory managers, and they indicated the number was concealed from the field – “nowhere in the company was there anywhere you could go and find out if your patients were still on drug.” Reps resorted to asking their doctors, and the discontinuation rates “caused alarm” with “a lot of patients...dropping off.” Ex-territory managers estimated discontinuation rates as at least 50%, and one alleged that the chief commercial officer confirmed the figure in late 2021.

**Harmony refused to provide sales reps with refill or discontinuation rates for their territories**
A: “The red flag, in my opinion, is the lack of transparency to refill rates—in most of the companies that I've worked for, there was an incentive, a paid incentive, to pull the drugs through and keep people on drug. **Nowhere in the company was there anywhere that you could go and find out if your patients were still on drug.**”
Q: “Did you ask? Did you try to figure that out?:
A: “Oh, absolutely yeah. Many, many times.”
Q: “What would they say?”
A: “The data is not available. The only person I really asked my immediate supervisor. She didn't know. They'd constantly say we'll find out for you. But the only way that I would know is to be asking physicians, "Hey, is that patient on drug?" …nowhere at Harmony is that information available.” – Former territory manager in an eastern state

**Discontinuation rate caused alarm among reps**
“The other thing that caused alarm for me was - so I had already signed on with them. I have a good friend who's a board-certified sleep specialist in Philadelphia. **I just asked, how many patients have you had on Wakix? And he said nine. I said, how many have stayed on the drug? It was one at that point.**” – Ex-Harmony territory manager for a large region in the northeast

“A lot of patients are “dropping off”
“In technical terms, they call them discontinuation. Basically, **a lot of patients are dropping off.**” – Ex-Harmony territory manager for a large region in the northeast

**Rep thinks discontinuation rate “would be closer to 50%” now**
“If I had to guess, I know it was at least 25% when I was in it, and I don't know what it is now, now that it's been out longer. I would think; honestly, it would be higher by now. **I would say it would be closer to 50%** unless they reduced the price and have given $0 coupons, which I don’t think they are.”– Ex-Harmony territory manager for a large region in the southeast across two states
An ex-territory manager stated that “the overwhelming sense in the company is that they are fudging the numbers” for patients on Wakix and discontinuation rates. He speculated that “patients on Wakix” counted referral forms faxed to the hub versus patients who were approved and actually on it, and that “no sales consultant has any transparency or visibility into how many patients are on drug in their territory. I have never seen that before in a pharma company.” He added that “the bottom of this will fall out…they’re going to get found out” as investors “squeeze” the company to explain the actual patient starts, patients on drug, and discontinuation rates.

“The overwhelming sense in the company is they are fudging the numbers.”
“Overwhelming” internal sense at Harmony that they’re “fudging the numbers”

“The overwhelming sense in the company is they are fudging the numbers.” I couldn’t really get a sense whether that - basically, they’re clouding, obfuscating, fudging the numbers around two things: how many patients are on drug at any one time and what is the discontinuation rate. Nobody that I talked to is privy to those numbers. What I thought was really interesting because it deviates from anything I’ve seen in specialty pharma… I think maybe on their earnings calls, they are referencing the number of patients that have formed new starts that were faxed in. So, they’re using that as a bellwether for a proxy for success. In the compensation structure, there is no component of the bonus tied to overall volume. So, the sales consultant have no skin in the game to keep a patient on drug, and, even more importantly, no sales consultant has any transparency or visibility into how many patients are on drug in their territory. I have never seen that before in a pharma company.” – Ex-Harmony territory manager for a large region in the northeast

Discontinuation rates and number of actual patients on drug would be alarming; “bottom of this will fall out”

“Let me add one thing. My sense, is absolutely…the bottom of this will fall out. They’re going to get found out at some point, or payors are going to bolt... my hunch would be, that the discontinuation rates at some point they’re going to get squeezed by investors, the market. Somebody’s going to kind of squeeze them for how many patients are you treating? How many patients are on drug? What are the discontinuation rates? So, that’s going to come out, and I think that could be alarming. And then insurance payors - at some point, they may push back and say this drug is just not worth it based on its therapeutic effect.” – Ex-Harmony territory manager for a large region in the northeast

Source: Scorpion Capital consultation calls with experts
The ex-territory manager continued that “it is so hidden – they’re going to enormous lengths…they’re blinding their sales consultants to patients…they’re investing no energy in the patient staying on the drug…none…that’s not a long term play.” He contacted a colleague still at the company for his sense of the numbers, stating that “his sentiment was it’s all bullshit…they don’t want anybody seeing or having access to or eyes on discontinuation rates and/or patients on drug.”

**Harmony going to “enormous lengths” to prevent reps form knowing number of patients**

Q: “They don’t want them to know the discontinuation rates?”
A: “Yeah, so imagine that the rep goes out, and the only thing they see is new starts for that quarter and if the patient went on drug. Now, it’s such a tiny window, and it is so hidden - they’re going to enormous lengths in my mind. And maybe I’m wrong, and maybe there are other companies that do this; I’d never seen it. They’re blinding their sales consultants to patients - basically, they’re investing no energy in the patient staying on drug. None. That’s not a long-term play…but these guys seem to be focused solely on just new starts and hiding all data from everybody.”

Q: “And how did your contacts interpret that? Is it that they don’t want the salesforce to get demoralized because most of their patients are dropping off? “
A: “The person I spoke to specifically gave me these details. Certainly, his sentiment was it’s all bullshit, and they’re trying to hide it in terms of, essentially, they don’t want anybody seeing or having access or eyes on discontinuation rates and/or patients on drug. There’s no other way to interpret that…The big takeaway is that the salesforce is not incentivized in any shape or form to keep patients on drug, to sustain volume. It is purely a new patient machine, how many forms you’re getting across the finish line—how many forms are you getting into the hub and how many are going on drug? It’s all very short-term.” – Ex-Harmony territory manager for a large region in the northeast

Source: Scorpion Capital consultation calls with experts
Harmony was founded in 2017 by Jeff Aronin, the company’s Executive Chairman. A family trust is the second largest holder, with 18% ownership worth ~$500MM. It is a one-trick pony whose sole commercial asset and source of revenue is the US license to an old, toxic drug called pitolisant, marketed as Wakix, that no reputable pharma company would touch – alchemically transformed into $2.5B market cap and 6X LTM revenue. Pitolisant was developed by and licensed from Bioprojet, a small and questionable French lab, which received EMA approval in 2016 and the FDA in 2019. Bioprojet’s opaque French filings suggest the drug face-planted in Europe. Wakix is a once-daily pill indicated for the treatment of excessive daytime sleepiness (EDS) and/or cataplexy in adults who have narcolepsy. We note the label’s specificity: it is not a cure for narcolepsy, a very rare disease, and merely addresses two symptoms in people with the condition.

*Wakix package insert and consumer website - www.wakix.com*

———INDICATIONS AND USAGE———

WAKIX is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy (1)

Harmony’s commercial landscape is difficult for two reasons. First, narcolepsy is ultra-rare at 0.04% of the US population and cataplexy is rarer still at 0.005% - in other words, only ~10% of narcoleptics have it. Cataplexy is vaguely defined as “sudden and transient episodes of loss of motor tone triggered by emotions.” Narcoleptics are not collapsing on the street like cataplectic goats when tickled, as attacks are brief at seconds or minutes, “self-limiting and resolve without medical attention,” often barely perceptible such as a twitch of an eyebrow, and the symptom is well-handled with SSRI’s. Second, the market for EDS - Wakix’s only other market opportunity besides cataplexy - is crowded with numerous approved drugs, such as amphetamines (Adderall), methylphenidates (Ritalin), modafinil and its variants, antidepressants like SSRI’s, sodium oxybate’s like Jazz Pharma’s Xyrem and Xywav, and solriamfetol (Sunosi). Our doctor interviews indicate no shortage of options.

Table of drugs for narcolepsy/EDS/cataplexy

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples with EMA/FDA approval states (with brand names)</th>
<th>Treatment Indications</th>
<th>Recommended Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>• Amphetamines salts (Adderall) &lt;br&gt; • Dextroamphetamine (Dexedrine, Zenith) &lt;br&gt; • Methylphenidates (Ritalin) &lt;br&gt; • Dexamfetamines (Fortid) &lt;br&gt; • Lorcaserin (Vernix)</td>
<td>• excessive daytime sleepiness &lt;br&gt; • sleep attacks</td>
<td>5-60 mg of amphetamine salts (sometimes split doses) &lt;br&gt; 20-40 mg of methylphenidate</td>
</tr>
<tr>
<td>Wakix-like, Promising Agent</td>
<td>• Modafinil (Provigil) &lt;br&gt; • Armodafinil (Nuvigil)</td>
<td>• excessive daytime sleepiness &lt;br&gt; • sleep attacks</td>
<td>100-400 mg (sometimes split doses)</td>
</tr>
<tr>
<td>Sodium Oxybate</td>
<td>Gammahydroxybutyrate (approved for EDS and cataplexy: Xyrem*)</td>
<td>• excessive daytime sleepiness &lt;br&gt; • sleep attacks &lt;br&gt; • cataplexy &lt;br&gt; • sleep glycinia &lt;br&gt; • hypnagogic hallucinations &lt;br&gt; • disturbed nocturnal sleep</td>
<td>4.5-9 g (split dose at night)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>• TCA’s (Clomipramine, Imipramine) &lt;br&gt; • SSRIs (Paroxetine, Citalopram) &lt;br&gt; • SNRIs (Effexor, Pristiq)</td>
<td>• cataplexy &lt;br&gt; • sleep glycinia &lt;br&gt; • hypnagogic hallucinations</td>
<td>Varies</td>
</tr>
<tr>
<td>Benzodiazapines: Hypnotics</td>
<td>(Trazodone, Ambien)</td>
<td>disturbed nocturnal sleep</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Harmony’s dilemma is obvious – in a crowded field, what’s the value proposition, particularly at ~$175,000/year? It is not a cure for narcolepsy, and of the two symptoms it is approved for, cataplexy is ultra-rare, not serious, and easily treated. That leaves EDS – excessive daytime sleepiness – which unfortunately has countless treatments. The standard of care and first-line treatment is typically modafinil, a CNS stimulant available as a generic for $10-15/month or under brand names like Provigil, or its longer-acting variant armodafinil (Nuvigil, FDA approved for EDS in narcolepsy). Doctors then step-through and/or combine antidepressants, stimulants, and sodium oxybate. Comically, even the clinical trials show Wakix is inferior to modafinil, which leaves only one conceivable argument: that it is easier to prescribe because it’s not a controlled substance, the flimsy thread by which its FDA approval, commercial pitch, and stock narrative hangs.

*Modafinil on Amazon Pharmacy - $10-15/month with Amazon Prime*

*Wakix.com patient and physician sites push the non-controlled angle – excerpts*

WAKIX is the first and only FDA-approved treatment for people with narcolepsy that is not a controlled substance.
The DEA classifies drugs from schedule 1 to 5: doctors prescribing have to register with the DEA, and they can only prescribe for 1-6 months at a time, depending on its scheduling. Modafinil is schedule 4, which means a physician can write a 6 month supply – making Wakix’s value proposition dubious – and even amphetamine-based stimulants can be prescribed for a 90-days. Unfortunately for Harmony, every single physician we interviewed indicated there is no value proposition to Wakix being non-controlled: 1) prescribers are already registered to write controlled substances; 2) they still have to write periodic refills for Wakix patients as it’s a third or fourth line drug, almost never used as a monotherapy, and other drugs in the cocktail are controlled. And of course, as it’s only a Hail Mary add-on to scheduled drugs, it’s not displacing and reducing the use of any controlled substance. We preview color from a later section:

“Absolutely no benefit from it”; “it doesn’t matter”
“I don’t think there’s any big deal because, for me, I’ve still got to prescribe medicine, so I see absolutely no benefit from it… you have to prescribe something anyway; it’s just a couple of clicks. So, I don’t know what the big deal is… so, Wakix is less scheduled, but it doesn’t matter.” – Neurologist, sleep specialist, and professor at leading West Coast institution

“I don’t see” any value from it
“I prescribe a lot of scheduled—like whether it’s Adderall or modafinil or like all of these. It’s a little bit of a hassle because you do have to plug in an extra code when you write these controlled substances, but at the same time, as a doctor, you want to give a medication that works because then, I mean, first of all, it’s about the patient. You want to improve their health. You want to improve their condition. And second of all, if you’re a doctor prescribing medications that don’t even work, I mean, what type of value is there? What kind of value is there? I don’t see it.” – Sleep physician in great Los Angeles area

“It’s not that big a deal”; scheduled substances can still be prescribed for up to 6 months at a time
“Schedule 3 and Schedule 4 can both be written with refills going as much as 6 months. My Xywav prescriptions, I have to refill twice a year, the same thing with modafinil. So, it’s not nearly as onerous as Adderall, where you have to write a new script every month… Schedule 2s are more annoying. Three and 4 are the same, honestly. It’s not that big a deal... most patients I treat with narcolepsy are going to be a 2 or 3-agent regimen, and those are going to involve things that are at least Schedule 4.” – Physician and medical advisor to Harmony

Source: Scorpion Capital consultation calls with experts
Harmony’s schtick is that Wakix – a histamine H3 receptor antagonist/inverse agonist - is a “first-in-class molecule with a novel mechanism of action specifically designed to increase histamine signaling the brain by binding to H3 receptors.” Histamine involvement in immune and inflammatory responses is well known, but it also acts as a neurotransmitter. The simplistic – and since disproven – theory behind Wakix is that anti-histamines can cause drowsiness, so a drug that increases histamine levels should increase wakefulness. There are 4 known histamine receptors: H1 and H4 are involved in allergic responses, the former targeted by OTC anti-histamines; H2 modifies gastric reflux; and H3 is primarily expressed in the CNS. By purportedly binding to the H3 receptor, Wakix claims to block histamine from binding to it and thereby increasing its level.

**Harmony S-1**

**Pitolisant is a histamine H3-receptor antagonist/inverse agonist that enhances the activity of histaminergic neurons in the brain.**

1. Pitolisant binds to presynaptic H3 autoreceptors, which blocks histamine binding to these receptors and increases histamine release from presynaptic neurons.
2. Acting as an inverse agonist, pitolisant initiates increased histamine synthesis and release from vesicles in the synapse.
3. The increased histamine in the synapse is then available to bind to excitatory postsynaptic H3 receptors.
4. Increased histamine binding at H3 receptors results in an increase in neuronal firing of postsynaptic neurons.
5. Increased firing of histaminergic neurons further activates wake-associated brain regions and further inhibits non-REM and REM sleep-associated brain regions.

HA = Histamine; HDC = L-Histidine decarboxylase; H3R = Histamine 3 Receptor; H1R = Histamine 1 Receptor


Source: https://www.sec.gov/Archives/edgar/data/1802665/000119312520217849/d755703ds1a.htm
Pitolisant is the first and only H3 receptor antagonist/inverse agonist on the market for a reason – virtually every major pharma company tried to develop one for decades, with a 100% failure rate due to a fatally flawed mechanism of action and pharmacokinetic profile, lack of efficacy, and toxicity. The elephant in the room is self-evident: how did a small French lab miraculously succeed when over a dozen global pharma players failed, and why did no other pharma company license it until Jeff Aronin came along? Pitolisant’s structure was published in 2002 and we think it was first synthesized in the 1990’s, meaning it sat for a quarter-century with no takers. The compound is so old that the three patents Harmony asserts are a sham. We located a 2002 paper that published the molecule’s structure under a different name, creating prior art that would instantly invalidate the IP if we challenged in an Inter Partes Review.

Jean-Charles Schwartz paper submitted for publication in 2001 - table shows same molecule as pitolisant
Development of a New Class of Nonimidazole Histamine H3 Receptor Ligands with Combined Inhibitory Histamine N-Methyltransferase Activity
Joachim Apelt,† Xavier Ligneau,† Heinz H. Pertz,† Jean-Michel Arrang,§ C. Robin Ganellin,∥ Jean-Charles Schwartz,§ Walter Schunack,† and Holger Stark*†
Received October 31, 2001; Revised Manuscript Received January 10, 2002

Chart 1. Histamine H3 Receptor Antagonists and Inhibitors of HMT

FUB 649 is identical to pitolisant

Source: https://pubmed.ncbi.nlm.nih.gov/11855993/
Harmony has **no intellectual property**, which is besides the point as no reputable pharma company would market a drug this toxic and risk existential tort litigation, but at the very least it **removes any possibility of acquisition** – already remote as the 3 US patents expire in 3, 6, and 7 years, respectively. We nonetheless asked a biotech IP litigator – someone with decades of experience and who we have consulted for years – to review each US patent. Bioprojet knew that their prior publication of the molecule’s structure would be problematic, and hence asserted in the US patents that they had invented a novel salt of the molecule – pitolisant hydrochloride – and that the previous molecule was merely a base. The **lawyer** indicated the tactic is spurious and that an IPR would be prejudicial against the company, as it establishes an attempt to mislead the patent office. He stated it is damning that the authors on the US patents are the same as the ones in the 2002 paper; and that even then, PubChem shows the patented salt published as prior art in 2006, and perhaps earlier if one commissions a search from the American Chemical Society’s database.

**Inventors listed on patents are the authors of 2002 paper**

(54) MONOHYDROCHLORIDE SALT OF 1-[3-[3-(4-CHLOROPHENYL) PROPOXY] PROPYL]-PIPERIDINE

(75) Inventors: Manuel Raga, Barcelona (ES); Juan Sallares, Barcelona (ES); Marta Guerrero, Barcelona (ES); Antonio Guglietta, Molins de Rei (ES); Jean-Michel Arrang, Dourdan (FR); Jean-Charles Schwartz, Paris (FR); Holger Stark, Bad Homburg (DE); Walter Schumack, Berlin (DE); Xavier Ligneau, Saint Gregoire (FR); Jeanne-Marie Lecomte, Paris (FR); Charon Ganellin, Thame (GB)

**PubChem shows 2006 prior art for the HCL salt**

Pitolisant Hydrochloride; 903576-44-3; Ciproxidine; BF 2649; Pitolisant HCl; ...

- Compound CID: 11551689
- MF: CgH22ClNO
- MW: 332.3g/mol
- IUPAC Name: 1-[3-[3-(4-chlorophenyl)propoxy]propyl]piperidine hydrochloride
- Isomeric SMILES: C1CCN(CC)C(CCC)(C)CC2=C(C(=C(C2=C(=C(C1Cl))))Cl)Cl
- InChIKey: XLXfKeCj1RMp0A0S-UHFFFAOYSA-N
- InChI: InChI=1S/C17H26ClNO.CH/c18-17-9-7-16(8-10-17)6-4-14-20-15-5-13-19-11-2-1-3-12-19/9-7-10H1-6,11-15H2,1H

Create Date: 2006-10-26

A biotech with no IP is, of course, a house of cards - typical of a Jeff Aronin rig. Aronin is a serial biotech promoter with a notorious history. His fetish for dressing up and pushing toxic CNS drugs seems to have begun in his youth. He was interviewed by a local radio station in 2021, where he stated his first job out of college was selling a pediatric epilepsy drug for Carter-Wallace. The interviewer notes that “he was upset to see the company pull off the market a therapy that…helped many families because a side effect was discovered.” We presume the drug was felbatol, which was implicated in fatalities and remains one of the most infamous cases of post-approval toxicity. It is one thing to be a naïve drug rep in his early 20’s – quite another to be a 55-year old who still has a grudge about it.

Jeff Aronin, Harmony founder and executive chairman

Carter-Wallace Issues Epilepsy Drug Warning

NEW YORK — Drug maker Carter-Wallace Inc. told doctors Monday to take their patients off the epilepsy drug Felbatol after two people who took it died from a serious form of anemia, a development that led to the company’s stock losing a third of its value.

Aronin has bent over backwards to avoid being the public face of Harmony, for reasons we shall explain, preferring to call the shots as Executive Chairman with a family trust as the #2 holder. He has a full-blown PR effort to portray himself as a responsible member of society. Websites like www.jeffaronin.com detail his purported philanthropy, presumably to push unflattering articles to the second page on google. Virtually every bio highlights the Aronin Family Foundation, which claims to support every cause under the sun – economic development, community parks, arts & culture, youth wellness, sports, and faith based organizations. Foundations are required to file an IRS form, yet we could locate no evidence of the foundation’s existence on the IRS database, nor of any grants beyond a small, local biotech incubator that appears to be a business activity.

Foundation’s website – www. Aroninfoundation.org

IRS search for tax-exempt organizations – no results for the search term “aronin,” aronin foundation,” etc.

Aronin’s bio’s, websites, and his LinkedIn profile all avoid mention of Marathon Pharmaceuticals, which he founded a decade ago. The company spent $370K to license old clinical data, from the 1990’s in the UK, for a Duchenne Muscular Dystrophy drug called deflazacort, a cheap generic sold for ~$1,000/year, and used it to get FDA approval without running any trials. The day it was approved, Marathon raised the price by ~90 times to $89,000 versus the price US families paid an online UK pharmacy. The WSJ, in a detailed investigative piece, stated “the company didn’t do the late-stage clinical trials needed to win FDA approval to market deflazacort. That step usually is the costliest part of drug development and often cited by companies as a justification for their prices.”

**WSJ article, 2017**

**Revolt Against Sky-High Drug Prices Prompts a Pioneer to Cash Out**

Sticker shock over $89,000 muscular-dystrophy treatment from Marathon Pharmaceuticals and shame campaign against CEO led to hasty sale
Aronin’s actions caused widespread outrage, leading to his expulsion from the board and membership of PhRMA, the top pharma lobbying organization. Prior to Marathon, Aronin employed the same price-gouging strategy at Ovation Pharmaceuticals, buying old drugs and, per the WSJ, raising “prices of five of the drugs by an average of 1,360%.” The FTC unsuccessfully sued Ovation, with the headline of the press release accusing it of “illegally acquiring drug used to treat premature babies with life-threatening condition” and that “unlawful acquisition resulted in nearly 1,300% price hike.”

**Marathon/Aronin press coverage**

**CEO Under Fire for $89,000 Drug Has a History of Steep Price Hikes**

Source: https://www.bloomberg.com/news/articles/2017-02-14/marathon-ceo-placed-steep-price-hikes-on-drugs-before-emflaza?leadSource=verify%20wall

**Marathon ‘pauses’ launch of $89,000 muscular dystrophy drug in United States amid pricing outrage**


**Under Fire over Price, Marathon Sells Duchenne Drug Emflaza to PTC**


**PhRMA expels 22 members with new R&D rules as it works to burnish its image**

Aronin sparked bipartisan furor and two investigations in Congress. GOP senator Tom Cotton called it “nothing short of outrageous” in a speech on the floor, and one on an FDA oversight committee criticized that Aronin “found a way to game the system.” A separate group of Democrat senators published a letter demanding information. Bernie Sanders and Elijah Cummings held a hearing. The WSJ noted that “Mr. Aronin refused to provide much of the information requested by congressional investigators” and that he “declined to attend a November 2014 hearing organized by Messrs. Cummings and Sanders, citing travel outside the U.S… Mr. Aronin’s absence was noted with an empty chair and a placard with his name on it.”

**Empty seat chair with Aronin’s name, and Congressional press conference as part of the aftermath**

Jeffrey Aronin declined to attend a Senate hearing in November 2014 about rising drug prices, citing travel outside the U.S., but was shaken by having his name called out at the hearing.

Sen. Bernie Sanders, an independent from Vermont, and Rep. Elijah Cummings (D, Md.) at a news conference about the cost of prescription drugs in September 2015. Marathon’s drugs became part of a broader investigation by the two lawmakers.

Aronin’s company Castle Creek follows his usual playbook, similar to the one for Harmony: licensing an old, toxic foreign drug and trying to win FDA approval for a rare drug indication in order to spike the price. Valor Equity Partners and Fidelity are principal investors in both Harmony and Castle Creek. The EMA restricted the drug in 2013 due to liver toxicity – a cheap osteoarthritis drug called diacerein, which Castle Creek reformulated as an ointment for a rare skin disease, for the self-evident purpose of price gouging. The phase 2 failed, but articles indicate the company planned to press ahead with a phase 3 anyway.

2018 article on Castle Creek, and EMA warning for the drug below

Fresh from a $72M raise, Jeff Aronin's new lead rare disease drug is flagged as a failure

In Castle Creek’s case, they took an old drug that is marketed in a variety of countries around the world for osteoarthritis — 50 mg diacerein — and reformulated the IL-1 beta anti-inflammatory drug into a topical treatment for an ultra-rare fragile skin disease called epidermolysis bullosa.

PRAC recommends suspension of diacerein-containing medicines
Committee cites concerns over gastro-intestinal side effects and liver toxicity

Source: https://endpts.com/fresh-from-a-72m-raise-jeff-aronins-new-lead-rare-disease-drug-is-flagged-as-a-failure/
Harmony licensed pitolisant from a French lab called Bioprojet, run by an idiosyncratic scientist named Jean-Charles Schwartz, who spent decades hunting for an H3 drug like Captain Ahab after Moby Dick, with little to show for it until Jeff Aronin showed up. We spoke with various sources who shared troubling anecdotes of his scientific approach and personal conduct. A European KOL called him “crazy,” but demurred when we asked for specifics. Others were more forthcoming, such as a scientist who spent decades at a global pharma company, publishing hundreds of papers including foundational work on the H3 receptor. His knowledge of pitolisant was in-depth, and he described his interactions with Schwartz - “an odd sort of guy” - and recounted a story of his shouting from the audience at presenters at conferences – “It was bizarre. I’d never come across that before.” He described him as paranoid and “getting into screaming matches” and “shouting matches” with scientists at international meetings – “he did it to somebody from Novo Nordisk”; “he attacked a guy from GSK…it’s just insane.”

Anecdotes of Schwartz’s behavior

“That would describe Jean-Charles. It was really fundamental research that he published. But then, after a while, it’s like, well, so what? It was a great discovery, but it doesn’t make you a pharmaceutical company, right? When I showed up, the first talk I gave was in the Netherlands on what we were doing…and at the end of the talk, he shouted from the audience. He said how can I have the nerve to come to Europe and not acknowledge all the work that they did? And I was just stealing all their science. He did that in a public forum. And he did it to somebody from Novo Nordisk, who was talking in the lecture before and then two years later, he attacked a guy from GSK. It’s just insane. And I’d never had this at a scientific meeting…there was a degree of arrogance there.. It was bizarre. I’d never come across that before…he was always very dismissive of other pharmaceutical companies, and I had a couple of shouting matches with him over some of the science because he felt he was the owner of H3. He had actually—he characterized the receptor. He got two nice papers in Nature, I believe. But he was a—I don’t want to be pejorative about—he had this arrogance about him… When pitolisant came out—I remember going to international meetings and getting into screaming matches with these guys because they felt they had everything and all the big pharma companies would rip them off, which was not the case—Ex-longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience.
Schwartz is exactly the sort of guy we short, and we think that pitolisant is the product of a 20-year pattern of scientific and clinical dishonesty by Bioprojet and the inner circle that shows up on key papers and trials. As an example, we excerpt the 2007 pilot study, the foundational paper for pitolisant, which contains a cunning, nefarious trick to conceal the danger of elevated and variable plasma levels of the drug, given its dose-dependent relationship to QT prolongation. The paper states that 5 of 22 patients had elevated plasma levels >150 ng/mL, but doesn’t disclose how elevated. Yet the paper is written to convey the impression that the average plasma level is far lower: “the plasma level average 100.6 + 78.1 ng/mL (n=17).” Note the insertion of “n=17” – in other words, the study had 22 patients, but Bioprojet excluded the five with plasma levels >150 ng/mL in the calculation, making it impossible to deduce how high it went – as absurd as a fund manager reporting average returns but excluding the five biggest losers.

*Pitolisant pilot study, first published in 2007, indicates massive plasma level variability*

An inverse agonist of the histamine H₃ receptor improves wakefulness in narcolepsy: Studies in orexin⁻/⁻ mice and patients

Tiprolisant dosages were performed at the end of the treatment period with a median sampling time at 3.75 h after the last drug intake. The plasma level average was 100.6±78.1 ng/ml \(n=17\). Elevated plasma levels (>150 ng/ml) were observed in 5 patients, in some cases related to the experience of adverse events occurring a few hours after drug intake.

Source: https://pubmed.ncbi.nlm.nih.gov/18295497/
By 2015, having blown 15-20 years looking for an H3 drug and with every major pharma company giving up on the class and moving on, we think Bioprojet was in financial distress and Schwartz was desperate. We spoke with an ex-employee in France, who stated Bioprojet hadn’t been able to make payroll for two months and staff were leaving. He was involved in monitoring clinical trial sites, including HARMONY 3, a key trial in support of FDA approval – and the color he provided was explosive. He stated that a significant percentage of patients in HARMONY 3 presented elevated liver enzymes – consistent with the experience of other H3 programs; that two trial investigators escalated the issue, which occurred at “three or four sites”; that he then escalated it to Bioprojet “upper management,” who were “worried” as it could put their pending EMA application at risk; and that Bioprojet decided to prematurely halt the study for the “welfare of the patients.” The trial was packaged neatly into a paper that makes no mention of the alleged hepatic signal and early termination, and declared a success. We first note the ex-employee’s role, and then share detailed color on the next pages:

**Ex-Bioprojet employee played key role in overseeing clinical trials**

“I worked on Harmony 3. I also worked on the study on [redacted]. It was another study in the nervous system. In fact, this study occurred in France. We used to work with [redacted]. I also worked on another study beginning with [redacted]. But the last study, which I speak about, where the studies are in the starting phase. In fact, I took part in the regulatory submission at the beginning of the project—I took part in the management of a different CRO, responsible for the management of the study… I worked with the hospital [redacted] in South of France, and I worked with a clinic in [redacted]. I worked in one hospital in [redacted]. And I worked with one hospital in [redacted] near Paris. I worked with [redacted] in Paris. I think that’s it. There were seven sites, but I remember all of the sites. We worked with Dr. [redacted], and we worked with Dr. [redacted] who is a very important doctor in the discipline.” —Former Bioprojet employee

Source: Scorpion Capital consultation calls with experts
The ex-employee stated that 8 patients out of 102 on pitolisant exhibited the issue. He was not able to recall which enzyme or details of the labwork, given the trial was conducted 2011-2016 per ClinicalTrials.gov. The expert was a French speaker whose English was mediocre, but we view the information as credible as his color regarding which trial sites and investigators reported the adverse event was specific, as were his recollections of meetings with Bioprojet management. He stated the investigators checked the calibration of their lab equipment to verify the finding, and then pressed Bioprojet for a plan and a decision – “it was a difficult moment because we were trying to get the [EMA] marketing authorization…upper management was worried about that…to protect the welfare of the patients, it was decided to stop the study….but because the marketing authorization was in danger.”

Ex-employee listed the trial sites which had issues, and stated the EMA approval was in danger
Q: “Do you remember the names of the sites who the doctors were that observed the liver problem—which sites?”
A: “Yes, it was Dr. [redacted].”
Q: “So, he observed some liver side effects?”
A: “Exactly, yes. And the other was—the site where the problem was observed was [redacted] with Dr. [redacted]”
Q: “And what did she say about the drug?”
A: “She decided to review the calibration of the machine to be sure that the bad blood result observed was due to the product. She asked for a plan and the upper management of Bioprojet decided to stop the study.”
Q: “What was her reaction?”
A: “You know it was a difficult moment because we were trying to get the marketing authorization. The upper management of Bioprojet was worried about that. To protect the welfare of the patients, it was decided to stop the study. But because the marketing authorization was in danger.”
Q: “And what did the doctors say when they brought it up? They said I have these blood results - they don't look good?”
A: “The bad result was declared as an adverse event. At first, they decided to review the calibration of the machine to be sure the problem did not occur from the machine. But when it had been confirmed that, in fact, the bad blood result was observed – it was to report it, they asked us, Bioprojet for a plan but Bioprojet, they decided to stop the study.”
Q: “So, what did the doctors say? They said the patient is having blood problems - I'm worried?”
A: “Yes, they sent an alert about the problem. They said we observed a bad blood result. What is your decision?” – Former Bioprojet employee

Source: Scorpion Capital consultation calls with experts
We asked a number of times on the call who made the decision to halt the trial, and he stated it was upper management, which we interpret to be Jean-Charles Schwartz. He indicated that he conveyed the findings to management in a meeting – “yes, they were worried, yes.”

Management was allegedly worried and decided to halt the trial
Q: “You said 8 patients had a problem with the bloodwork for their liver. In that trial, there were about 100 patients.”
A: “102 patients…but the end of the study, we observed this problem with the blood result. And it was preferable to stop the study.”
Q: “Were they worried? They were worried because the data might look bad?”
A: “Yes, they were worried, yes.”
Q: “The problems with the bloodwork, did that happen all at one site? Or did it happen at other sites?”
A: “It happened with three or four sites.” – Former Bioprojet employee

The ex-employee shared the finding with upper management, who allegedly stopped the study
Q: “Was it your decision to shut off the study or somebody else’s decision?”
A: “No, it was upper management’s decision. It was an upper-management decision. I observed different sites with different patients with the bad blood result. So, in a meeting I had with upper management, I told them what I observed with this result, and we decided to stop the study.”
Q: “What did management say when you brought it up? What was their reaction?”
A: “They were surprised. There was a medical director that thought that it was maybe a bad reaction of the product, maybe it could concern a problem, trouble, so it was preferable to stop the study. We saw bad effects, we stopped the study.”
Q: “Are you positive the blood levels were related to a liver enzyme?”
A: “Yeah, yeah, yes, yes. It was preferable to stop the study, yes.”
Q: “But because of the liver?”
A: “Yes, exactly, yes.” – Former Bioprojet employee

Source: Scorpion Capital consultation calls with experts
Our interviews with ex-Harmony executives and others indicated concern inside Harmony about Bioprojet’s data, and that they even they didn’t trust it. An ex-senior employee in a medical liaison role stated “we’re lucky to have FDA approval...put it that way,” stating Harmony was “surprised at how they did the trials...it was really poor”; “there were holes in the data...we dug deeper in to the analyses...the way they ran the analyses was unconventional, not to FDA standards”; “I was surprised the FDA didn’t have an issue with it.” When we asked if Harmony was worried about getting approval, the ex-employee simply replied “Oh yeah. Oh yeah. Oh yeah.”

Harmony was worried about Bioprojet data and FDA reaction to it
A: “Jean-Charles Schwartz discovered the histamine 3 receptor, and he discovered a molecule to target it, and then built a company around it. He had no idea what he was doing, no idea what he was doing. He has no idea how to commercialize pharmaceuticals. We were more surprised about how they did the trials. It was really poor. We’re lucky to have FDA approval. Put it that way.”
Q: “Were you guys worried about getting approval?
A: “Oh yeah. Oh yeah. Oh yeah.”
Q: “What were you guys worried about?
A: “There were holes in the data. We dug deeper into the analyses. The way they ran the analyses was unconventional, not to FDA standards. Bioprojet didn’t even want to talk to the FDA to figure out a pathway to approval...the data wasn’t all there. There was missing data for some of the outcomes, and they actually put some assumptions with the analyses, and the FDA accepted it.”
Q: “Was there anything that you recall that people were nervous about in the data as far as these holes?”
A: “Yes, for cataplexy endpoints, we used—not we—Bioprojet used a specific statistical analysis called "geometric mean." And in that analysis, it allowed for you to input zeros when you had missing data. So, looking at that and looking at so much of the missing data, I was surprised the FDA didn’t have an issue with it because that’s a measurement that you don’t typically use that measurement for analysis.” -Ex-senior employee in a medical liaison role

Source: Scorpion Capital consultation calls with experts
We asked a KOL who has served a medical advisor to Harmony, and who appears to have interacted with the company and/or FDA during the pitolisant NDA process. He stated Bioprojet was less than forthcoming in sharing data with Harmony, and that they’ve had “a very difficult relationship with” Schwartz. His color was telling: that they’re “like these little tinkerers working in their shop and sort of puttering along”; that Bioprojet “couldn’t find” files when asked”; and “if you had something like that from Merck, it would be horrifying.” He then laughed and wondered out loud if Bioprojet were “like FTX” or “intentionally doing criminal stuff” or “just basically naïve and being idiotic.”

Harmony had difficulty getting data from Bioprojet, which is “like a small lab”; “little tinkerers working in their shop”

“I remember in the early days when Harmony was set up as a company, I remember them expressing to me, it’s like, “Oh my gosh, it’s harder for us to get the data from Bioprojet than we thought it was going to be.”...I just remember them griping about how they thought it was going to be a slam-dunk just to get the data, send it into the FDA, and then it took twice as long as they thought it was going go...I think Bioprojet like a small lab. I really have no idea, but I wouldn't be all surprised if their staff consisted of 10 people or something like that. And so, but I don’t know. In the early days of modafinil, it was made by this French company called Laboratorie Lafon, which is another small, family-run company, and it's exactly the same kind of thing. It was just like these little tinkerers working in their shop and sort of puttering along and doing okay science, but they had no idea how to actually get to market.” -Neurologist and professor at a pre- eminent academic institution

Bioprojet couldn’t find files; would be “horrifying” if from Merck

A: “I just know from my discussions with Harmony that they’ve had a very difficult relationship with him because Bioprojet wasn’t really well-run, and so they had trouble actually—it took them a long time and a lot of headaches to get their package together for the FDA...my recollection, they were sort of asking for files and then Bioprojet was just really slow, or they couldn't find them. It was just kind of sloppy company stuff.”

Q: “So, there are two ways one could interpret that. One is that they're just slow and sloppy. The other is that whenever I encounter companies that are like, oh, we had a missing sample in our study, it's typically a huge red flag.”

A: “I have to say, if you had something like that from Merck, it would be horrifying because it's like these guys should know their stuff. Honestly, I look at this as just [chuckles]... like FTX, the question is, were these people intentionally doing criminal stuff or were they just basically naïve and being idiotic?” -Neurologist and professor at a pre-eminent academic institution
Wakix sales are fueled by a handful of speakers who receive payments from the company. A table from CMS OpenPayments lists the top ten recipients below. We interviewed six of them, in detail over 60 minute phone consults. We have done hundreds of doctor calls over the years, as part of our research into healthcare frauds, and have never encountered ones as reckless and blatant as the ones who prescribe Wakix at scale. It is clear that reputable doctors at leading, prestigious academic centers won’t touch the drug or at best dabble, as we learned from two KOL’s at Harvard and Stanford. The list below is populated by private practice doctors in locations not known for their research excellence - Huntsville, AL; San Ramon, CA; Dublin, OH; and so forth. We found it shocking that even these speakers are ambivalent about Wakix, all of them jamming it in as a 3rd or 4th line drug in combo – not one of them even pretended to love it during our calls, with comments like “a subtle effect” as the best they could muster.

Top recipients of payments from Harmony per CMS OpenPayments database

Source: https://openpaymentsdata.cms.gov/company/100000786822
The sleep space has long been known as a cesspool for reimbursement fraud for sleep-test studies or sleep therapy equipment, with one DOJ prosecution after another and has been highlighted in reports by the HHS Office of Inspector General as one of the worst pockets of billing abuses. The #1 recipient of payments from Harmony is Haramandeep Singh, who we believe to one of their highest volume prescribers and most prolific speakers. In 2010, a “Dr. Haramandeep Singh dba Sleep Medicine Specialists of California” was one of several defendants named in a qui tam action pursuant to the False Claims Act. The primary defendant (not Singh) settled for $11MM with the DOJ, and claims against Singh and the other defendants appear to have been dismissed.

Filings related to qui tam case and eventual settlement

Oxygen Equipment Provider Pays $11.4 Million to Resolve False Claims Act Allegations

| CONSTA SLEEP CENTER, LLC, | ) |
| DRS. KIRIT PATEL, JAGJEET KALRA, | ) |
| AND RON KASS, D.B.A. | ) |
| HAYWARD BB SLEEP DISORDERS CENTER, DR. MAN KONG LEUNG, D.B.A | ) |
| PACIFIC COAST SLEEP DISORDERS | ) |
| AND DR. HARAMANDEEP SINGH, D.B.A. SLEEP MEDICINE SPECIALISTS OF CALIFORNIA | ) |
| Defendants | ) |

OIG report on abuses, and examples of numerous prosecutions in the sleep space

Sleep Disorder Clinics – High Use of Sleep-Testing Procedures  

Former Owner of Sleep Study Clinics Pleads Guilty to Fraud, Tax Charges  

Two Charged with Running $11 Million Sleep Study Scam that Billed UPS and Costco Health Care Benefit Programs for Unneeded Tests

The recklessness that high volume Wakix prescribers exhibited in our interviews was jarring, a reflection of the false sense of safety created by Harmony’s sales practices. The FDA erred in approving the drug, but still slipped in a few watered-down warnings that understate the risk. However, one speaker after another told us they ignore them entirely. The clear pattern of the drug’s toxicity, combined with extensive comorbidities in narcoleptics like obesity, diabetes, and cardiac issues, sets the stage for disaster. We quote two prolific speakers near the top of the OpenPayments list, who stated they are most responsible for educating doctors in the US about Wakix, and whose comments are representative. The first: “those items are just warnings...you’re not going to run into those issues hardly ever”; “I’ve never ordered an EKG...that’s what I tell doctors, these are just warnings...technically speaking, you don’t have to do anything...you can just prescribe it, which is what we do.” A second: “I do not run any EKG’s...I don’t check lab work...remember, most narcoleptics are...pretty damned healthy...”

Bay Area-based speaker

“These items are just warnings. You’ve not going to run into those issues hardly ever. I mean, to date, I’ve never ordered an EKG on a patient. That’s what I tell doctors; these are just warnings. I think the biggest thing is a doctor is going to know if a patient has severe hepatic impairment or not. That’s just obvious. And then, if someone has QT interval prolongation, you’re going to be followed by a cardiologist. But you don’t run into those issues. There are so many medicines already out there that cause QT prolongation that don’t even have it on their label, and this is just this company being very conservative. Will it impact prescribing? To some degree, yes—some doctors may be more hesitant to prescribe it or want to take all the precautions before they do anything, but technically speaking, you don’t have to do anything. You can just prescribe it, which is what we do.”

Alabama-based speaker

“I do not run any EKG’s. When a patient says they’ve got things that are like palpitations or they feel dizzy, and by the way, that’s never happened in my clinic, then we would tell the patient to stop, and we’d do a cardiology referral or ER or whatever. There are a lot of drugs out there that prolong QT. Some antibiotics, some antidepressants do. I mean, you don’t run EKGs—most doctors that I’m aware of don’t do EKGs before putting them on an antibiotic. So, I don’t routienly do that. I don’t check lab work. Remember, most narcoleptics that we see are pretty damned healthy people. […] No, I don’t do lab work.”

Source: Scorpion Capital consultation calls with experts
>A dangerous molecule in a drug class plagued by toxicity and FDA recalls
Histamine receptor antagonists have a long history of cardiotoxicity. The culprit is hERG channel blockade, a potentially fatal syndrome which is the most common reason for the FDA or a manufacturer to remove a drug off the market as well as the most frequent cause for drug discovery programs to fail. hERG is short for “human Ether-a-go-go-Related Gene.” Certain drugs inhibit its activity, leading to QTc prolongation, an abnormal hearth rhythm visible on an EKG. QT prolongation can cause arrythmia, a type of ventricular fibrillation known as Torsades de Pointes, and sudden death. A widely-cited paper in the New England Journal of Medicine listed a number of drugs withdrawn due to QT prolongation.

Drug-induced hERG blockade can lead to sudden cardiac death

Drug-Induced Prolongation of the QT Interval

In the past decade, the single most common cause of the withdrawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with polymorphic ventricular tachycardia, or torsade de pointes (Fig. 1), which can be fatal. Three structurally unrelated drugs that were marketed in the United States or elsewhere for a range of noncardiovascular indications have been removed from the market or had their availability severely restricted because of this rare form of toxicity. These drugs are terfenadine, astemizole, grepafloxacin, terodiline, droperidol, lidoflazine, sertindole, levomethadyl, and cisapride.

The literature on drug-induced hERG blockade and QT prolongation is extensive: “QT prolongation is one of the most infamous adverse drug reactions taught in pharmacy curricula because it can lead to sudden cardiac death.” Another paper indicates that “there is no threshold of QTc prolongation at which TdP [Torsades de Pointes] is certain to occur, and that each 10-ms increase in the QT interval contributes “to approximately 5% to 7% exponential increase in risk.”

Drugs withdrawn from market due to QT prolongation share similarities with pitolisant

Drug-Induced QT Prolongation And Torsades de Pointes

TdP, an uncommon polymorphic ventricular tachycardia, is characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line on an electrocardiogram. TdP is associated with QTc prolongation, which is the heart-rate–adjusted lengthening of the QT interval. QT prolongation is one of the most infamous adverse drug reactions taught in pharmacy curricula because it can lead to sudden cardiac death. Drug-induced prolonged repolarization of the heart is represented by a prolonged QT interval and can predispose a patient to develop this life-threatening arrhythmia. There is no threshold of QTc prolongation at which TdP is certain to occur. A QTc greater than 500 milliseconds (ms) has been associated with a twofold to threefold higher risk for TdP, and each 10-ms increase contributes to approximately a 5% to 7% exponential increase in risk. QT prolongation can increase hospital length of stay and all-cause mortality in patients. In addition, many drugs have the potential to cause QT prolongation and/or TdP, either alone or in a drug interaction situation.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481298/
The NEJM paper is a seminal one but published in 2004, and listed nine drugs withdrawn as of then due to cardiotoxicity and QT prolongation. Two of the nine were histamine receptor antagonists, as is pitolisant, and the molecular structure of all three is defined by a piperidine ring, the significance of which we shall explain. Most of the others that were recalled also have other troubling similarities to Harmony’s drug. Another four of the nine either involved histamine antagonist activity or targeted adjacent neurotransmitters: droperidol was a dopamine receptor antagonist but had histamine antagonist activity; sertindole was a dopamine and serotonin antagonist; cisapride was a serotonin receptor antagonist; and lidoflazine, which contained a piperazine ring in its molecular structure - closely related to the piperidine ring in pitolisant and which has similar binding behavior.

Drugs withdrawn from market due to QT prolongation share similarities with pitolisant

Drug-Induced Prolongation of the QT Interval

In the past decade, the single most common cause of the withdrawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with polymorphic ventricular tachycardia, or torsade de pointes (Fig. 1), which can be fatal.1 Nine structurally unrelated drugs that were marketed in the United States or elsewhere for a range of noncardiovascular indications have been removed from the market or had their availability severely restricted because of this rare form of toxicity. These drugs are terfenadine, astemizole, grepafloxacin, terodiline, droperidol, lidoflazine, sertindole, levomethadyl, and cisapride.

Source: https://www.washingtonpost.com/archive/politics/1997/12/30/seldane-to-be-taken-off-us-market-by-maker/69d37826-3c40-49b1-8167-06c9c8b191b0/
Of the two histamine receptor antagonists that were recalled, one was terfenadine which is now infamous as the poster child for fatal QT prolongation. It was introduced as Seldane in the US in 1985, the first prescription antihistamine for allergies. In 1990, the FDA issued a report on serious ventricular arrhythmias and forced the company to send an alert to all physicians. A black box warning followed in 1992, the same time that it was discovered to have liver as well as cardiac toxicity, culminating with the FDA forcing the drug off the market in 1997.


The Hazards of Seldane

Seldane Should Be Taken Off Market, Fda Says Antihistamine Blamed For Deaths When Combined With Other Drugs

FDA proposes shelving Seldane; Drug company vows fight

SELDANE TO BE TAKEN OFF U.S. MARKET BY MAKER

After the Seldane/terfenadine debacle, the FDA is highly sensitized to QT risk, as are drugmakers who screen and eliminate development programs with any QT issue. While a number of older drugs have hERG/QT liability, it is extremely rare to see a new drug come to market with pitolisant’s flagrant cardiotoxicity and QT profile. It is critical to note that the absolute number of confirmed cases of QT prolongation and fatalities from Seldane was astonishingly small relative to its use. By 1990, five years after introduction, 100 million people had taken Seldane with only two reported deaths. By 1997 when it was recalled - 12 years after launch - the FDA had only “received about 40 reports of serious heart rhythm irregularities, evidently caused by Seldane, that led to eight deaths.” Given the anomalous number of adverse event reports associated with pitolisant – visible quickly after US launch a mere couple of years ago – the evidence demonstrates that its cardiotoxicity is exponentially greater than Seldane’s.

Only two Seldane-related deaths by early 1990’s despite 100 million people having taken the drug, per letter published in New England Journal of Medicine in 1993

Cardiac Toxicity of Terfenadine

One study reviewed cases of torsades de pointes, the severe ventricular arrhythmia associated with terfenadine intake, reported to the FDA. Of the 25 reported cases, two patients died and the others required hospitalization. The researchers found that it is the parent drug terfenadine, not its major metabolite, that blocks potassium channels, causing substantial prolongation of the QT interval. A prolonged QT interval is associated with torsades de pointes. Erythromycin and ketoconazole inhibit metabolism of terfenadine, leading to elevated concentration of the drug, which in turn is associated with prolongation of the QT interval.

Source: https://www.jwatch.org/jd199305010000002/1993/05/01/cardiac-toxicity-terfenadine
A letter published in the medical journal *The Lancet* summarized the number of adverse events reports for Seldane/terfenadine, as well for astemizole, the other histamine receptor antagonist that was pulled off the market – 98 cardiac deaths plus sudden deaths for terfenadine in 11 years, along with another 429 cardiac events such as ventricular arrhythmias, fibrillations, or tachycardia (elevated heart rate) – again, a seemingly infinitesimal percentage given >100 million patients who took the drug, but alarming enough for withdrawal. For astemizole the comparable figures were 8 fatalities and 110 other events. The vertical axis shows adverse events per million daily doses sold, which we shall next calculate for pitolisant to demonstrate its danger vs. both terfenadine and astemizole.

**Adverse event reporting rates for various histamine receptor drugs**

![Graph showing adverse event reporting rates](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(97)26018-6.pdf)

**Antihistamines reporting rates 1986–96 for cardiac rate and rhythm disorders, subset of these disorders, and death as a result of a cardiac rate/rhythm reaction or reported as sudden death**

*Arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolongation, supraventricular tachycardia, ventricular tachycardia, torsade de pointes. Numbers on bars are actual numbers of ADR reports. Terf=Terfenadine.*

Source: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(97)26018-6.pdf
It is straightforward to estimate and compare pitolisant’s adverse event reporting rate per million daily doses sold vs. terfenadine and astemizole. Harmony has reported $872 million in cumulative revenue since US launch in 2019, through Sep 30, 2022, which is the same date that the FDA adverse event data goes to, per the FAERS database. Assuming an average annual pitolisant price of ~$150,000 per year yields a daily price of $411. At one dose a day, $872MM divided by $411 equals 2.12 million daily doses sold. With one fatal adverse event in FAERS plus another six across clinical trials, we arrive at 2.83 fatal events per million daily doses sold – more than 100 times greater than the .025 shown below for terfenadine, and about 300 times greater than astemizole.

**Adverse event reporting rates for various histamine receptor drugs**

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**Antihistamines reporting rates 1986–96 for cardiac rate and rhythm disorders, subset of these disorders, and death as a result of a cardiac rate/rhythm reaction or reported as sudden death**

*Arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolongation, supraventricular tachycardia, ventricular tachycardia, torsade de pointes. Numbers on bars are actual numbers of ADR reports. Terf=Terfenadine.

Source: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(97)26018-6.pdf
Pitolisant’s cardiotoxicity and hERG/QT liability is not a surprise, for the same reason that Seldane and astemizole were recalled: drugs in the histamine receptor class are known to be the most prone to hERG channel interference and therefore uniquely dangerous. The clinical and drug chemistry literature is unequivocal – “the reason for this is that the pharmacophores of the hERG channel and histamine receptor show remarkable similarities.” A pharmacophore is a molecular model that characterizes how a drug binds to a receptor. Given the close structural similarity between the histamine receptor and the hERG channel, a histamine receptor antagonist like terfenadine or pitolisant has inherent off-target activity with hERG – that is, cardiotoxicity is a feature not a bug.

*Paper explains why histamine receptor antagonists are uniquely prone to hERG channel liability*

A number of drug discovery and development programs have been hampered by issues with drug induced cardiac arrhythmia. This is particularly well-known for histamine receptor antagonists, e.g., the potent human ether-a-go-go-related gene (hERG) channel blocker Terfenadine (Teldane®, Seldane®). Terfenadine is an H1 receptor 1996; Fenichel et al., 2004; Gintant et al., 2011), but hERG channel blockade has become the most frequent single cause for drug withdrawals (Fenichel et al., 2004), and many drug discovery programs have been delayed (imposing significant costs on the pharmaceutical company) or stopped due to hERG channel liabilities of potential drug candidates.

Bahl et al., 2012; Becknell et al., 2012; Hudkins et al., 2012; Moorthy et al., 2014). While compounds from very different chemical classes may interact with the hERG channel due to its relatively large hydrophobic pore, the property of hERG channel liability has been observed especially often for histamine receptor antagonists. The reason for this is that the pharmacophores of the hERG channel and the histamine receptor show remarkable similarities (Davenport et al., 2010).

Source: https://www.frontiersin.org/articles/10.3389/fphar.2014.00203/full
Pitolisant is inherently more cardiotoxic than terfenadine for another reason: terfenadine targeted the histamine H1 receptor, but pitolisant targets the histamine H3 receptor, and the pharmacophore of the H3 receptor is even more similar to the hERG channel. In other words, not only is the histamine receptor antagonist class already prone to QT prolongation via hERG blockade, but within this class, a histamine H3 receptor drug like pitolisant is uniquely more dangerous. We note a paper that compared the structure of H3 receptor drugs and their “significant similarity to the predicted pharmacophore for hERG blockers” and their “strong binding to the hERG kB channel” which “manifests itself in a dose-dependent QTc prolongation relationship” in animal models in a failed Abbott H3 receptor drug program.

**Paper explains the challenges from the similarity of the histamine H3 receptor and the hERG pharmacophores**

Using Electrophysiology and *In Silico* Three-Dimensional Modeling to Reduce Human Ether-à-go-go Related Gene K⁺ Channel Inhibition in a Histamine H3 Receptor Antagonist Program

**ABSTRACT**

The histamine H3 receptor (H3R) plays a regulatory role in the presynaptic release of histamine and several other neurotransmitters, and thus, it is an attractive target for central nervous system indications including cognitive disorders, narcolepsy, attention-deficit hyperactivity disorder, and pain. The development of H3R antagonists was complicated by the similarities between the pharmacophores of H3R and human Ether-à-go-go related gene (hERG) channel blockers, a fact that probably prevented promising compounds from being progressed into the clinic. Using a
The paper graphically details the obvious similarity between the histamine H3 receptor and hERG blocker pharmacophores, illustrating why an H3 antagonist like pitolisant is inherently high risk for QT prolongation and cardiotoxicity.

*Structural similarity between hERG blockers and H3 receptor inhibitors*

Compounds that inhibit the H3R with high affinity contain a basic amine linked to an aromatic or general lipophilic region that is connected to either (1) a second basic site, (2) a polar group, (3) a lipophilic region, or (4) an acidic group\(^{12,19-21}\) resulting in pharmacophores that comprise significant similarity to the predicted pharmacophore for hERG blockers (Fig. 1).\(^\text{22}\) As an example, Abbott’s preclinical candidate ABT-239 (Table 1) is reported to exhibit strong binding to the hERG K\(^+\) channel (Ki = 0.45 nM; 420-fold selectivity H3R/hERG), which manifests itself in a dose-dependent QTc prolongation in dog (Altenbach, personal communication) and monkey.\(^\text{18}\)

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![Image](https://pubmed.ncbi.nlm.nih.gov/21133680/)
More importantly, the paper explained the unsolvable fatal flaw and Catch-22 for a histamine H3 drug like pitolisant: if the drug is tweaked to have less affinity for the hERG channel, then that “dramatically affects[s] its on-target activity” and “high inhibitory affinity” for the H3 receptor – there is no way to win. There is no way to thread the needle and bind to the H3 receptor but not to the hERG channel – so again, cardiotoxicity is a feature, not a bug, and explains one of the many reasons why virtually large pharma company went after the H3 receptor for more than two decades – with a 100% failure rate due to lack of efficacy or toxicity.

**Adverse event reporting rates for various histamine receptor drugs**

Using Electrophysiology and *In Silico*
Three-Dimensional Modeling to Reduce Human
*Ether-à-go-go* Related Gene K⁺ Channel Inhibition
in a Histamine H3 Receptor Antagonist Program

The obvious goal of a H3R drug discovery program, therefore, is to design molecules that have high inhibitory affinity for the H3R but not for the hERG channel. But changing/removal of a whole pharmacophore point from a molecule series is likely to dramatically affect its on-target activity, especially in the case of H3R, where the target and hERG pharmacophore maps are so similar. In this article,
A key driver of pitolisant’s hERG-related cardiotoxicity is the piperidine ring in its molecular structure. The medical chemistry literature is unequivocal in highlighting piperidine’s propensity to cause hERG blockade. Piperidine is an organic compound with the formula \((\text{CH}_2)_5\text{NH}\), a six-member ring with five methylene bridges (-CH\(_2\)-) and an amine bridge (-NH-) where one of the carbons is replaced by nitrogen. In the next few pages, we detail three separate papers that describe piperidine’s massive hERG liability and the role of the nitrogen atoms in particular.

_Piperidine ring structure per Wikipedia_  
_Molecular structure of pitolisant_

The first paper – by NIH researchers - screened more than 4,000 drug molecules to determine which factors drive drug-induced hERG blockade and QT prolongation. Ominously for pitolisant, the top factor identified in the hERG model was a “nitrogen atom in a saturated ring, like piperidine....” The scientists then validated the model with drugs known to have hERG liability, and it accurately predicted the hERG liability of several histamine-receptor drugs that were recalled. Terfenadine was predicted to have a 62% probability of being hERG active, and astemizole was 94%.

*Paper on piperidine structures in drugs*

**Prediction of hERG Liability**

The top five important features extracted from the training set of hERG model included N16 (a positively charged nitrogen atom in a saturated ring, such as piperidine or piperazine), C3 (an aromatic carbon atom with no substitution and adjacent to two aromatic carbon atoms), H2 (a hydrogen bonded to an aromatic carbon), M13 (a number of aromatic rings), and S5 (sulfur in a ring bonded to two aromatic atoms). These features summarize the two key characters of the hERG blockers – an aromatic moiety and a positive charge center, which is in good agreement with commonly recognized pharmacophore models of hERG blockers. Compounds containing two N16 nitrogen atoms have a greater than 73% chance to block hERG channels, and the probability dropped sharply to 10% for compounds without an N16 atom (Figure 9a). Piperazine and piperidine are two moieties frequently used by medicinal chemists to manipulate molecular flexibility and hydrophobicity. However, both structure features have high potential to trigger undesirable hERG activity, unless the basicity of the ring nitrogen atoms is alleviated by introducing neighboring aromatic rings or carbonyl groups.

*Table excerpts show accurate prediction of hERG liability in recalled histamine-receptor drugs*

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5382096/
A second paper further elaborated on the nitrogen atom in the piperidine ring as core of the problem and its “profound influence on the binding and structural recognition of a piperidine-containing drug.” The nitrogen atoms “tend to be more promiscuous in vivo and can show cardiovascular tox, driven by interaction with the hERG potassium ion channel and phospholipidosis.”

**Paper on piperidine structures in drugs**

The modulation of the basicity of the nitrogen atom can have a profound influence on the binding and structural recognition of a piperidine-containing drug and often fluorine substitution is used to this end.\(^2\) For example the Merck kinesin spindle protein (KSP) inhibitor shown below (R= 4-fluoro 4-aminopiperidine) exploit a number of times in drug discovery.\(^2\) Molecules containing basic nitrogen atoms tend to be more promiscuous in vivo and can show cardiovascular tox, driven by interaction with the hERG potassium ion channel, and phospholipidosis.\(^4\) Incorporation of fluorine has been used as a strategy to modulate the pK\(_a\) of an adjacent basic nitrogen atom and in doing so disrupt binding to the the hERG ion channel and increase cardiovascular safety in vivo. To discovery chemists, fluorine and piperidine are a dynamic duo that can have the potential to get them out of deep water. The challenge is bringing them together.

Source: https://www.scientificupdate.com/process-chemistry-articles/syn-3-fluoro-4-aminopiperidine-a-story-from-multiple-orientations/
A third paper was published in Science and states that piperidine “turned out to be more trouble than it was worth” and that it “can set off hERG activity, which can (in some cases) lead to hearth rhythm problems, which can (in pretty much all cases) lead to your drug wiping out. And maybe taking you with it….” – “everyone would be worried about what might happen when the stuff hit the general population.”

Another Funny-Looking Structure Comes Through

That piperidine is the polar add-on, but it turned out to be more trouble than it was worth. Some of the medicinal chemists in the audience will be saying “hERG”, and they’re right. Piperidines and piperazines are great structures, and medicinal chemistry would be a lot poorer without them, but they can set off hERG activity, which can (in some cases) lead to heart rhythm problems, which can (in pretty much all cases) lead to your drug wiping out. And maybe taking you with it, depending on just how bad things got. hERG is one of those things that we didn’t used to understand very well, and arguably still don’t, but we understand just enough about it to make trouble for ourselves. Many older compounds made it onto the market with hERG activity in them, but no one is going to feel comfortable developing a compound with strong activity on that ion channel now, for fear of what might happen in the clinic. Even if it were to make it through, no one would feel comfortable sending it off for approval, for fear of what the FDA would make of it, because everyone would be worried about what might happen when the stuff hit the general population. Some hERG stuff can be dealt with via more predictive animal models (dogs wired for telemetry, with constant monitoring of heart rate), but a compound with lotsa hERG may not even get that far.

Source: https://www.science.org/content/blog-post/another-funny-looking-structure-comes-through
>Pitolisant’s origin: an old, failed compound no reputable drug company would touch
Harmony licensed pitolisant from a small lab in France called Bioprojet. Our investigation reveals Bioprojet’s multi-decade attempt to develop a histamine H3 receptor drug, resulting in one utter failure after another – including pitolisant. From our review of every paper published by Jean-Charles Schwartz going back to the 1990’s, we were startled to discover that pitolisant is an ancient compound, first synthesized a quarter-century ago. We unearthed a Schwartz paper from 2001 that includes a table with H3 receptor candidates, including a molecule then named FUB 649 – which we noticed is identical to pitolisant – which of course also means it’s too old to have any intellectual property protection left.

Jean-Charles Schwartz paper submitted for publication in 2001: table shows same molecule as pitolisant

Development of a New Class of Nonimidazole Histamine H3 Receptor Ligands with Combined Inhibitory Histamine N-Methyltransferase Activity

Joachim Apelt,† Xavier Lignseau,‡ Heinz H. Pertz,† Jean-Michel Arrang,§ C. Robin Ganellin,‖ Jean-Charles Schwartz,§ Walter Schunack,† and Holger Stark*†

Received October 31, 2001; Revised Manuscript Received January 10, 2002

Chart 1. Histamine H3 Receptor Antagonists and Inhibitors of HMT

Source: https://pubmed.ncbi.nlm.nih.gov/11855993/
The long and twisted timeline of pitolisant papers and trials is damning, suggesting that Bioprojet was well aware of its myriad dangers and flaws and rejected it as their lead H3 candidate multiple times over a decade. Schwartz appears to have tested hundreds if not thousands of potential H3 receptor ligands, going back to the 1990’s. He even wrote a paper in 2010 documenting the challenges, noting one compound after another that failed due to toxicity or other reasons. He stated that thioperamide was the first H3-receptor compound, developed in 1987, but it “displayed hepatotoxicity.” Then Bioprojet developed ciproxifan “which had to be abandoned after toxicity tests performed by Bioprojet.” Tellingly, he stated that “drug companies remained essentially uninterested in this research.”

Jean-Charles Schwartz paper written in 2010

The histamine H3 receptor: from discovery to clinical trials with pitolisant

It became rapidly clear that this was not the case: the agonist was rapidly inactivated by first-pass hepatic metabolism, whereas thioperamide displayed hepatotoxicity, presumably attributable to its thioamide group. Hence, the program to design an H3R antagonist as a drug useful to improve wakefulness and cognitive deficits in the clinics was continued with Robin Ganellin being embarked in this European enterprise after he had become Professor at University College London. Hundreds of compounds were prepared and tested in our University laboratories, a number of which like ciproxifan (Ligneau et al., 1998) were extremely potent in vivo, but had to be abandoned after toxicity tests performed by Bioprojet. The program also produced [125I] iodoproxyfan, a highly sensitive radioprobe, and potent H3R agonists, for example, Imetit or BP2.94. Meanwhile, whereas drug companies remained essentially uninterested in this research, several other university groups succeeded in designing H3R ligands with high potency such as clobenpropit or GT-2331 (recently reviewed in Sander et al., 2008; Stocking and Letavic, 2008; Raddatz et al., 2010). Only the latter compound was apparently submitted to a clinical trial, in adult attention deficit hyperactivity disorder (ADHD), but the result was never disclosed and, instead of being an antagonist, its partial agonistic properties were thereafter discovered.
We find it revealing that pitolisant was synthesized as early as 2001, but Schwartz sidelined it for alternative H3 drug compounds like ciproxifan and many others, on which he published for years. The papers make it clear they screened each compound for toxicity and receptor affinity, and we presume pitolisant ranked poorly and hence was not chosen as the lead. By 2007, their papers suggest their lead compounds were failing left and right— and at that point they dusted the cobwebs off pitolisant and published the first paper on it. After writing a few more papers on pitolisant and running early trials, he appears to have rejected it yet again—suggesting it ran into the same problems. Several papers published *after* those on pitolisant indicated that Bioprojet had already moved on to other lead H3 receptor candidates. For example, a 2003 paper showed what was later renamed pitolisant alongside other drugs they chose instead, and then a 2008 paper stated their “lead structure” was one called FUB 637— not pitolisant.

2003 paper shows pitolisant next to multiple other compounds they chose instead

2008 Schwartz paper shows a different lead H3 candidate than pitolisant

The present report provides an account of the synthesis and pharmacological evaluation of the new histamine H₃ receptor ligands. Compound FUB 637 (Fig. 4), a potent histamine H₃ receptor antagonist tested in vitro (hKᵢ: 3.1 nM) and in vivo (ED₅₀: 3.7 ± 1.0), was taken as a lead structure.³⁶

We find a 2011 paper by Schwartz to be damning evidence that he had already soured on pitolisant by that point and was well aware of its cardiotoxicity - and we note a striking omission in the data that suggests an attempt to cover up the danger. The paper described a structure-activity scoring model that Bioprojet developed to predict hERG liability of various H3 receptor compounds. The mere fact that he wrote an entire paper dedicated to mitigating the hERG-related toxicity of H3 receptor ligands is telling – consistent with literature documenting the inherent hERG liability of the class. The paper shows the molecular structures of dozens of h3 receptor candidates they tested – yet we see no mention of pitolisant. Given that the paper scored each drug candidate along a measure of hERG binding, the silence on the hERG parameter for pitolisant is troubling. Moreover, the paper is explicit that their recent lead compound was “FUB2.922” – not pitolisant – and that it too failed due to cardiotoxicity. And in case their distaste of pitolisant wasn’t already clear, they then stated their new lead is “compound 17,” the structure of which is shown - which is again not pitolisant.

Excerpts from 2011 Schwartz paper on hERG liability of various H3 receptor compounds

Source: https://pubmed.ncbi.nlm.nih.gov/21802950/

By 2011, Bioprojet indicated they had a new lead – which was not pitolisant.
How did a random French lab’s molecule “work” where over a dozen major pharma companies failed?
Histamine H3 receptor antagonists/inverse agonists have a 40-year history of well-documented failure and toxicity, starting with thioperamide’s synthesis in 1987 and termination due to hepatic and other liabilities. Our review of the clinical literature indicates that virtually every global pharma company had an active H3 ligand development effort, starting in the 1990’s and peaking in the 2000’s, and that these efforts ended in the mid-2010’s after decades of failure. The papers document countless failed clinical trials and research efforts to solve intractable issues related to toxicity and efficacy. It is in fact difficult to find a major player that did *not* attempt an H3 program and fail, as the list of flops includes those by Pfizer, Merck, Astra Zeneca, Johnson & Johnson/Janssen, Abbott, Glaxo Smith Kline, Novartis, Sanofi, and Schering-Plough. A 2019 paper summarized these failures over the last 20 years - the “obstacles in developing these agents are emphasized” – written by a researcher who has extensively published with Schwartz and who we think may be a co-discoverer of pitolisant.

*2019 paper by a longtime collaborator of Bioprojet’s head, Jean-Charles Schwartz*

Histamine H3 receptor antagonists/inverse agonists: Where do they go?

**Abstract**

Since the discovery of the histamine H3 receptor in 1983, tremendous advances in the pharmacological aspects of H3 receptor antagonists/inverse agonists have been accomplished in preclinical studies. At present, there are several drug candidates that reached clinical trial studies for various indications. However, entrance of these candidates to the pharmaceutical market is not free from challenges, and a variety of difficulties is engaged with their developmental process. In this review, the potential role of H3 receptors in the pathophysiology of various central nervous system, metabolic and allergic diseases is discussed. Thereafter, the current status for H3 receptor antagonists/inverse agonists in ongoing clinical trial studies is reviewed and obstacles in developing these agents are emphasized.

Source: https://pubmed.ncbi.nlm.nih.gov/31028835/
The paper is one of many reviews in the H3 receptor antagonist/inverse agonist literature that documents the long list of failed pharma programs. It shows the various flavors of H3 drug candidates that each company attempted; the countless indications they tried for each candidate; and summarizes the failed clinical trials for every condition under the sun: sleep disorders like narcolepsy, allergies, ADHD, dementia, schizophrenia, pain, obesity, multiple sclerosis, etc..

For example, it shows that Abbot, J&J, Merck, Pfizer, and others all tried and failed in their H3R programs for narcolepsy and excessive daytime sleepiness.

Table of chemical structures of H3R antagonists/inverse agonists by Pfizer, Merck, Glaxo, Abbot, Astra Zeneca, and others

Small excerpt of table showing H3R drug programs by pharma company and indication, as well a pie chart of attempted clinical trials

Source: https://pubmed.ncbi.nlm.nih.gov/31028835/
Another table in the paper compares each company’s H3 receptor antagonist/inverse agonist candidates for drug likeness. Consistent with color we received from researchers at companies like J&J who played leadership roles in developing these compounds, the molecules are trivial to synthesize and extremely similar to each other. The table even includes pitolisant, which was then known as BF2.639, and the list of drug likeness properties shows its similarity to other failed drug candidates in the space.

Table of drug-likeness properties across various H3 receptor antagonists/inverse agonists, with pitolisant shown under its previous name “BF2.649”

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<th>Compound</th>
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Most pharma companies with an H3 receptor program documented their struggles and failures in published papers, and others announced trials and then went radio silent – an indicator of failure. For example, J&J published a paper in 2007 listing various compounds they tried since the 1990’s. They also initiated a phase 2 narcolepsy trial in 2007 which failed. Every other large pharma company’s narcolepsy trials or development programs were a bust as well. Glaxo had its own phase 2 narcolepsy study from 2006 to 2008, which was terminated. Pfizer’s compound failed a phase 2 for the same indication as pitolisant – EDS with narcolepsy.

**J&J paper in 2007 documented efforts since 1990’s**

**Histamine H₃ receptor antagonists: From target identification to drug leads**

Source: https://www.sciencedirect.com/science/article/abs/pii/S0006295206006976

**J&J failed phase 2 trial for narcolepsy**

**A Safety and Effectiveness Study of a Single Dose of JNJ-17216498 in Patients With Narcolepsy**

Source: https://clinicaltrials.gov/ct2/show/NCT00424931

**GlaxoSmithKline failed phase 2 trial for narcolepsy**

**Effectiveness Of The Drug GSK189254 In Treating Patients With Narcolepsy**

Source: https://clinicaltrials.gov/ct2/show/NCT00366080

**Pfizer failed phase 2 trial for narcolepsy with EDS**

**A Study Of A Novel Compound For Excessive Daytime Sleepiness Associated With Narcolepsy**

Source: https://clinicaltrials.gov/ct2/show/NCT01006122
The reasons for the industry-wide failure of these H3R antagonist programs over several decades are voluminous: poor pharmacokinetic characteristics due to lack of bioavailability and/or a failure to penetrate the blood/brain barrier; a variety of off-target effects; and a broad toxicity profile. In fact, the H3 receptor and its pharmacological interaction are poorly understood – a key reason being that there isn’t just “one” H3 receptor as it has 20 varieties called isoforms. In other words, H3 receptors are a class versus a single uniform target. The scientific understanding of these isoforms is primitive, and there has been little research into how different H3 isoforms interact with a single drug. A notable review paper evaluated virtually every compound tried by various pharma companies and attributed the failure to “the complicated pharmacology of H3R” and “over 20 existing hH3R isoforms, with some having a different pharmacological profile.”

Excerpts from a review paper evaluating virtually every H3R drug candidate that was attempted

New developments around histamine H₃ receptor antagonists/inverse agonists: a patent review (2010 – present)

Generally, H₃R as a drug target is not easy. So far, >20 years after identification of the receptor and >15 years after cloning it, non-of-ligand has entered into the market. The complicated pharmacology of H₃R makes this way difficult. Differences in results and species dependency (with largest between hH₃R and rH₃R) have hindered interpretation of preclinical studies. Also over 20 existing hH₃R isoforms, with some having a different pharmacological profile may hamper understanding of the action of H₃R ligands.

At first in the 1990’s, every pharma company large and small with an H3 receptor agonist program developed compounds with an imidazole \((\text{C}_3\text{N}_2\text{H}_4)\) ring, an obvious structure as histamine contains the same ring. However, every imidazole-based program was terminated due to problems crossing the blood/brain barrier; cardiotoxicity via hERG blockade, liver toxicity via cytochrome P450 inhibition; and other issues. By the late 2000’s, the field then migrated to non-imidazole-based compounds like pitolisant, only to discover that they too had the same problems. We note Bioprojet initially focused on imidazole compounds like ciproxifan, but then migrated to non-imidazole ones such as pitolisant. The literature on the toxicity and pharmacokinetic difficulties of both imidazole and non-imidazole-based H3R candidates is extensive. An example is the paper below which highlights “significant blockade of the hERG channel,” “QTc prolongation,” and “drug-drug interactions,” and “phospholipidosis.”

Excerpts from 2009 paper – challenges with imidazole-containing compounds...

The histamine H3 receptor as a therapeutic drug target for CNS disorders

Early H3R antagonists/inverse agonists that reached the clinic were imidazole-containing compounds, such as Gliatech’s clinical candidate GT-2331 (Table 1; Ciprolisant, Perceptin\textsuperscript{®} [38]), and have been previously reviewed [39]. The development of this class of imidazole-containing compounds was probably terminated because of the inherent risk associated with the inhibition of cytochrome P450 isoenzymes, resulting in unacceptable drug-drug interactions (DDIs) [40,41], as well as complex H3R pharmacology.

...and same issues with non-imidazole-based compounds like pitolisant

Whilst the majority of non-imidazole classes of H3R antagonists appear not to inhibit significantly the CYP family of enzymes, many H3R antagonist programmes have reportedly suffered from significant blockade of the hERG \(K^+\) channel [43–45] or have demonstrated the potential for phospholipidosis [43,46] or they have wrestled with P-gp substrate problems. As an example, Abbott’s pre-clinical candidate ABT-239 (Table 1) is reported to exhibit strong binding to the hERG \(K^+\) channel \((K_i = 0.45 \text{ nM}; 420\text{-fold selectivity H3R/hERG})\) that manifested itself in a dose-dependent QTc prolongation in dog (Altenbach, personal communication) and monkey [47]. In addition, the compound was also reported to cause phospholipidosis. The combination of these two factors is probably what led to the compound’s demise.
The paper attributes “one of the challenges with H3R receptor antagonist design” as being the “similarity between the H3 and hERG pharmacophores.” Another paper highlighted how these issues plague non-imidazole-based compounds specifically, such as pitolisant: “poor pharmacokinetic characteristics,” “poor blood-brain penetration,” “genotoxicity” (DNA damage), as well as the problems such as cardiotoxicity already described on previous pages.

**Challenges due to similarity of H3 and hERG pharmacophores**

As discussed above, one of the challenges with H3R antagonist design is overcoming the similarity between the H3 [49,59,60] and hERG [61] pharmacophores. The H3R requires a basic amine linked to an aromatic/lipophilic region that is connected to either: (i) a second basic site; (ii) a polar group or (iii) a lipophilic region (Fig. 2) [12,59,60], which makes the H3R antagonists prone to hERG inhibition and phospholipidosis [60] (Altenbach, personal communication). Therefore, every H3R antagonist programme should

**Same issues even with non-imidazole compounds such as pitolisant**

Recent advances in histamine H3 receptor antagonists/inverse agonists of unwanted effects. Some of the hurdles [25,32,65,66] described for the non-imidazole H3R antagonists are:

- phospholipidosis (excess phospholipids accumulate within the lysosomes of cells; e.g., JNJ-5207852; Figure 1)
- interactions with the hERG potassium channel (e.g., ABT-239; Figure 1)
- high plasma protein binding (e.g., ABT-239; Figure 1)
- poor blood-brain penetration (e.g., A-320436; Figure 1)
- genotoxicity (e.g., A-331440; Figure 1)
- high lipophilicity
- poor pharmacokinetic (PK) characteristics (e.g., JNJ-5207852; Figure 1) and
- CYP450 interactions (e.g., NNC 38-1202; Figure 1).

We note comments in a particularly damning paper by a researcher who collaborated with Jean-Charles Schwartz as far back as the 1990’s in trying to develop H3 receptor antagonist candidates, and who we believe may be a co-developer of pitolisant. He summarized the problems with non-imidazole structures – like pitolisant – and cited the extensive literature on the challenges.

2019 paper by a longtime collaborator of Bioprojet’s head, Jean-Charles Schwartz - excerpts

Histamine H\(_3\) receptor antagonists/inverse agonists: Where do they go?

Although there are growing bodies of research dealing with diverse non-imidazole based compounds, they are not free from obstacles in their development pipeline and hence the design of these compounds is complicated by various factors briefly discussed below. One of the problems in designing H\(_3\)R antagonist/inverse agonists is the affinity of these agents towards the hERG K\(^+\) channel, resulting in cardiotoxicity and originated from the similarity between the H\(_3\)R pharmacophore and hERG K\(^+\) channels (Gemkow et al., 2009; Lazewska & Kiec-Kononowicz, 2010; Łaźewska & Kiec-Kononowicz, 2014; Tiligada et al., 2009). Phospholipidosis is an additional concern for non-imidazole-based compounds containing two basic sites (Gemkow et al., 2009; Lazewska & Kiec-Kononowicz, 2010; Łaźewska & Kiec-Kononowicz,
Other pharma companies tested pitolisant and their color is damning
Although Harmony and Bioprojet claim pitolisant is effective and safe, our research uncovered devastating, long-buried evidence that other large pharma companies synthesized pitolisant and concluded that it is plagued by severe problems including cardiotoxicity - and that the claims in Bioprojet’s seminal paper could not be replicated in their labs or others. Although pitolisant was approved in the US in 2019, it is a quarter-century old compound - Bioprojet’s key papers were published in the mid-2000’s, and the trials upon which it received FDA approval are circa-2010. Most of the research in the space dates to the 1990’s and 2000’s, after which it fell off a cliff as pharma companies fled after widespread failures. As past of our forensic literature review, we first noted a few lines in a 2010 paper that indicated that “the development and druggability of tiprolisant (BF2.649)” has “been questioned, since it had limited oral bioavailability, was a potent inhibitor of CYP2D6 and hERG, and also had a high potential for inducing phospholipidosis….,” – tiprolisant was an earlier name for pitolisant.

2010 review paper on H3 receptor compound programs indicated threw cold water on pitolisant

Histamine H₃ Antagonists for Treatment of Cognitive Deficits in CNS Diseases

shorter brain residence time [44]. The development and druggability of tiprolisant (BF2.649 5), reportedly in Phase II clinical trials for a number of potential indications, including cognitive enhancement, have been questioned, since it had limited oral bioavailability, was a potent inhibitor of CYP2D6 and hERG, and also had the potential for inducing phospholipidosis, possibly due to the high clogP (4.8) [76].

Source: https://pubmed.ncbi.nlm.nih.gov/2016960/
The paper cited a 2008 publication by scientists at Abbott, which we located and is one of the most cited in the field – and we further spoke to a scientist who was closely involved in Abbott’s efforts, which we shall detail. The authors make it clear that they synthesized pitolisant in their lab, as the structure had already been published. Their comments are remarkable and indicated that pitolisant is a total failure on all dimensions: pharmacokinetics, efficacy, and safety. They state that the 84% oral bioavailability claims in Bioprojet’s key 2007 paper – absurdly, only based on an animal study – “were not replicated in our lab (with 30, 5, and 2% bioavailability in mice, rat, and dog).” They add that “this limited oral bioavailability questions the data related to the ability of BF2.639 to increased histamine brain levels after oral administration” as well as their claims in another key paper. They further indicate severe toxicity: “our laboratory findings suggest that CYP2D6 inhibition, potent hERG binding and the potential for phospholipidosis would likely be important hurdles.”

2008 paper by Abbott researchers indicates they tested pitolisant and that it was a disaster

Pharmacokinetic parameters measured by a radioreceptor assay indicated that BF2.649 exhibits 84% oral bioavailability in mice. However, these data were not replicated in our lab (with 30, 5 and 2% bioavailability in mice, rat and dog). One recent report indicated a 2-h half-life and good brain penetration in mice using a superior analytical assay but no detailed pharmacokinetic parameters were provided (Ligneau et al., 2007a). This limited oral bioavailability questions the data related to the ability of BF2.649 to increased histamine brain levels after oral administration in mice and the EEG studies conducted in cats. Further studies these species. BF2.649 is presently under clinical investigation in several Phase II trials for the treatment of schizophrenia, ADHD, dementia and Parkinson’s disease. (www.stanleyresearch.org/programs/trialgrants.htm). From the development point of view, our laboratory findings suggest that CYP2D6 inhibition, potent hERG binding and the potential for phospholipidosis would likely be important hurdles for this novel compound.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2483387/pdf/bjp2008147a.pdf
Abbott’s comments were echoed in a 2009 paper by scientists at Evotec, a major drug development player that works with most of the world’s largest pharma companies. They indicated that they synthesized pitolisant in their laboratory, then known as BF2.649: “in vitro profiling in our laboratory (and others) suggests that BF2.649 has both a CYP 2D6 liability (IC50 = 0.4 mM) and potent hERG K+ channel blockade (IC50 = 0.49 mM).” They further indicated it has a poor pharmacokinetic profile with extremely low bioavailability.

2009 paper by Evotec researchers indicates they tested pitolisant and that it was a disaster

The histamine H3 receptor as a therapeutic drug target for CNS disorders

H3R antagonists/inverse agonists currently undergoing clinical evaluation

BF2.649 (tiprolisant)

Bioprojet’s H3R antagonist BF2.649 (Table 2) exhibits potent binding to native human (IC50 = 5.3 nM), rat (Ki = 17 nM) and mouse (Ki = 14 nM) cortical H3 receptors. Further in vitro profiling in our laboratory (and others [15]) suggests that BF2.649 has both a CYP 2D6 liability (IC50 = 0.4 μM) and potent hERG K+ channel blockade (IC50 = 0.49 μM). BF2.649 is also reported to have poor PK profiles in both rat and dog (5% and 2% bioavailability, respectively [15]). Despite these issues, BF2.649 has been extensively profiled in pre-clinical animal models [62] and progressed into the clinic. Bioprojet recently reported the first clinical evi-
We then consulted senior scientists from three major pharma companies - Abbott, Johnson & Johnson/Janssen, and GSK – who worked on similar H3 receptor antagonist/inverse agonist drug development projects. In two cases, they appear to have independently synthesized and studied pitolisant as a comparator. Despite years of effort, all three companies faced insurmountable challenges, such as bioavailability, drug variability/instability, blood-brain penetration, and toxicity, leading to the failure of their respective programs. The scientists provided detailed, consistent, and devastating evidence, describing the issues as unsolvable and inherent to this class of drugs. All three were intimately familiar with pitolisant and criticized it for having the same fatal flaws, based on their analysis or testing, and characterized it as an old, simple, and inferior compound compared to the molecules they developed – and which still failed. We begin with color by an ex-executive/senior scientist at Abbott, now at another major pharma company, who stated that they had an extensive H3 development program that “never went anywhere” – specifically for narcolepsy – despite their decades-long experience with histamine receptors given Abbott’s H1 agonist drug betahistine.

Abbott had an extensive H3 receptor program that “never went anywhere” – specifically for narcolepsy
A: “At Abbott, we had historically worked a lot on a histaminic receptor. We had betahistine, which is an H1 histaminic agonist that we have it in vertigo. We were researching this specifically in insomnia and narcolepsy.”
Q: “And this is H1 or H3 that you were studying for insomnia and narcolepsy?”
A: “We have H1 on the market already, and we started H2 and H3, and specifically, H3 we very interested in narcolepsy, which is a chronic sleep disorder.”
Q: “When did Abbott start the H3 program?”
A: “We had one since even before I joined the company. I think it started very early discovery in 2012.
Q: “And did it ever go anywhere?”
A: “No, it never went anywhere.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company
The ex-Abbott scientist indicated he was personally involved with multiple attempts with various H3 compounds over many years, which generally failed in phase 1 pharmacokinetic studies and used similar doses to pitolisant. The studies are unpublished, but he shared the findings and some data: 1) lack of bioavailability in the blood as “it degrades very quickly into metabolites”; 2) failure to pass the blood-brain barrier; and 3) massive plasma variability of drug from patient to patient, which he indicated was >300% but provided data suggesting it can vary by more than 10-fold, far past the toxicity threshold.

Compounds were so poor that always failed in phase 1 PK studies
A: “When we stopped, we stopped directly after the Phase I pharmacokinetic-pharmacodynamic studies. We didn't go any further after that. We did a PK study in 2017-2018.”
Q: “Was this published anywhere?”
A: “No, it's not published.”
Q: “So, there was a PK study. Were you involved with that PK study? Or you were just aware of it?”
A: “Yes, I was involved.”
Q: “I see a paper here, 2012. Safety, Tolerability in Pharmacokinetics of the Histamine H-3 Receptor Antagonist, ABT-288. Is that the same thing as pitolisant or the one you did?”
A: “That's a predecessor. That's why I told you it started in 2012. That's a predecessor from the optimized compound. We took it to clinical, Phase 1 later on, six years, and it failed again.”

Variability is 300% from patient to patient, up to >10X; tried similar dose ranges as pitolisant studies
A: “We went from 3 milligrams up to 90 milligrams in the PK study.”
Q: “And then what happened from 3 to 90? What did you observe?”
A: “…your main problem is around basically the active substance present in the blood and then passing the blood-brain barrier to allow efficacy because it degrades very quickly into metabolites, and the variability is almost 300% intersubject.”
Q: “How did you determine the variability? What did you guys measure to come to these conclusions?”
A: “It's very simple. This basically was an oral, and we did also an intravenous. We looked at the blood concentration of the metabolite. And we looked at the C-max, the T-max, the area under the curve after you get the patient to take this tablet. And you can see what the concentration is in the blood specifically after 15 minutes, it varies very much when you are absolutely seeing like 6 nanograms of metabolite and up to 25-75 nanogram. I don't remember exact data anymore - but that's basically the concentration in the blood varies between patients completely. The PK study was twelve healthy subjects normally. It was a center in Switzerland.”

Source: Scorpion Capital consultation calls with experts
Abbott faced problems in passing the blood-brain barrier in rodents, primates, and humans - “you don’t reach where the receptors are.” The “huge variability” in drug concentration in the blood – in human subjects, where some would see “a good peak” - was another flaw that led them to terminate the program, as they knew it was unsolvable from their long experience in the histamine receptor space. He stated pitolisant has the same bioavailability and variability issues.

Blood-brain barrier prevented the drug from reaching the receptors; saw this in animals, primates, and humans; variability in humans was a fatal flaw that led them to terminate the programs
A: “Then in animals - we didn't do that in humans - we looked at how it passed the blood-brain barrier and how much landed into the brain. This is by post-mortem extraction. And that's where you look at the problems with variability in passing the blood-brain barriers, so the effect is not reached because you don't reach where the receptors are.”
Q: “So you did an animal study as well, and then you dissected the animals to see how much of the active compound passed the blood-brain barrier.”
A: “We have to actually do at least two species before going into humans.”
Q: “So, the PK study, was that in humans or animals?”
A: “Both. We did it in rats first, then we did non-human primates, and then we went in humans.
Q: “Okay, you did it with rats, then you did it in primates, and then you did it in humans.”
A: “Correct.
Q: “You observed the same thing in humans that you saw in the animal models that it wasn’t getting past the blood-brain barrier?”
A: “Correct. The only difference is when we have an animal model with narcolepsy, then we saw an effect on the animals, which meant that it would maybe work in humans. But when we saw the huge variability in humans, then basically, we stepped out because we know that problem from the H1 histaminic agonistic from the betahistine, and we know that this will not work out further.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Variability is a key flaw in addition to lack of bioavailability; led to “some patients who see a good peak”
Q: “I'm looking at the FDA review for pitolisant, and it says, following oral administration of pitolisant 35.6 milligrams once daily, the study states Cmax and AUC is 73 ng. When they say 35 mg and the Cmax is 73 nanograms/ml, is that saying that there's almost no bioavailability?”
A: “Yes, that's correct. But the other problem is also variability.”
Q: “The data says, "pitolisant is moderate-to-high inner subject PK variability to 40% to 60%.” You're saying that's not true?”
A: “It can be true but with a huge variability plus or minus 100%. I think that's the problem, right? Occasionally, you get some patients who see a good peak.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Source: Scorpion Capital consultation calls with experts
The ex-Abbott scientist indicated that the bioavailability problems are inherent to all drugs in the class due to first-pass metabolism by CYP3A4, an enzyme that degrades the drug in the gut and liver before it enters general circulation or the brain – “metabolism is the biggest problem you have here.” We note pitolisant is specifically indicated as being metabolized by CYP3A4. He shared data indicating that “the bioavailability…is between 1 and 3% in blood and the fraction in the brain is less than 0.2%,” meaning that there is basically no unmetabolized drug left for a therapeutic effect as “90% of this drug just goes into the urine after all.”

**Bioavailability is caused by drugs in the class (like pitolisant) being metabolized by CYP3A4, which degrades the drug into metabolites before it can enter the plasma and brain**

A: “The biggest problem with this class is with the CYP3A4 having a very narrow therapeutic margin, and metabolism is the biggest problem you have here. That's the enzyme that actually degrades it. That's actually the pathway in which the product is degraded, so it's in metabolites.”

Q: “I see on Wikipedia, "It's an enzyme in the body in the liver and the intestine. Oxidizes small, foreign, organic molecules such as toxins or drugs." It's part of the cytochrome P450 family.”

A: “And that's why you will see with these products, *even pitolisant, they are very sensitive for any enzyme co-administration because all of these things are going on the same pathway.*” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

**Only 1-3% bioavailability in the blood and less than 0.2% in the brain; 90% of drug quickly metabolized into urine**

A: “The most important thing is where is the active metabolite. And do you have enough concentration for the active metabolite to really saturate the receptor? Because the problem with H3 receptors is they are everywhere. The H3 receptor exists in many places. The most important one is the brain, but you need a certain level of saturation to really reach the point that you're going to see an effect, that this patient starts waking up again or keeping enough attention.”

Q: “When you say you only observed 1% to 3% availability, is that in the bloodstream, or in the brain or both?”

A: “No, I'm talking first about the bloodstream, about the blood, the plasma. That's the first thing. And then the second thing you need to think about is how much of that is reaching the brain. You cannot test that in humans, but you can test that in animals.”

Q: “What did you observe in the blood serum versus the brain in the rodents and the primates?”

A: “As I said, the bioavailability is anything between 1 and 3% in the blood, and the fraction in the brain is less than 0.2%.”

Q: “Okay, there's basically no way that it can have an effect in the brain then.”

A: “Yes. And then 90% of this drug just goes into the urine after all. And that main metabolite pathways are ones like CYP3A4.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Source: Scorpion Capital consultation calls with experts
Abbott spent almost a decade trying to solve the pharmacokinetic and bioavailability issues in the program and couldn’t, illustrating the severity of the problems in the H3 class – “this was no surprise to anyone.” He indicated that even though they escalated doses from 3mg all the way to 90mg – similar dosages to those in the pitolisant studies - they still observed almost no bioavailability.

Q: “So, you just dosed 12 people one time in the clinic. You saw the massive variability, and you were like - this thing is dead on arrival?
A: “Exactly. So, it's four doses, and you take three patients, three healthy volunteers, and then if there is no toxicity, the next three was the highest dose and so on and so on until you reach your 12.”
Q: “So, you gave 3 to 90, and what were the middle doses?”
A: “We went up to 90, so we went, I think, from 3 milligrams, 15, 30, 60, and 90.”
Q: “And you just observed 1% bioavailability in each of those doses, essentially?”
A: “Yeah, that was the most important for us to really understand how the drug is distributed and released in the body.”
Q: “And what was your personal reaction? The reaction at Abbott? Were you guys like, wow, this thing is a disaster? How was this program viewed?”
A: “No, I don’t think, because we have the experience, as I said, from betahistine. And we had a lot of discussions ourselves about do we want to repeat some of the PK and the Phase 2 of the dosage finding of betahistine, which is our H1 receptor in vertigo. And we knew that for a long time. This was no surprise for anybody. The disappointment was that we were trying to fix the 2012 problem until 2017-2018, and we didn't manage to fix it. So, the disappointment was okay. This is R&D life, as usual.”
Q: “You said you guys spent six years on the program that basically failed?”
A: “Correct, but it’s good it was killed at this stage because at that stage the spending is very limited.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company
The ex-Abbott scientist stated they actually synthesized pitolisant and tested it as a comparator, and that it had the same fatal flaws as H3 receptor candidates they developed internally: “they didn’t solve the problem, and we didn’t solve the problem.” He indicated that pitolisant exhibited the same lack of bioavailability; that “the variability was very similar to our compound”; and that “we didn’t see much of it passing the blood-brain barrier…I remember it was around 3-4%, something in that range maximum, with very high variability.” He said that because of Abbott’s history with histamine-based drugs like betahistine that “we know this is unsolvable…we just gave up,” noting that this is “an area where there a lot of products failing one after another” due to toxicity and other issues.

Abbott tested pitolisant and it exhibited similar flaws around bioavailability, variability, and blood-brain barrier penetration

Q: “And then, did you guys try to figure out a way to solve this bioavailability problem, or you weren't able to solve it?
A: “No, we will not be able to solve. We tried with betaistine and didn't solve it. We know this is unsolvable. We just gave up.”
Q: “So, you’re saying it’s an unsolvable problem. Did you guys study pitolisant and the pitolisant papers as part of this program? Did you read those?”
A: “We tested it in our labs for some time as a comparator, also to compare the toxicity, and this we do very frequently. Like when we're looking at drugs in that category, we look at the toxicity comparison with a different product on the market or a different product from the competition. And we even synthesize it ourselves at this time.”
Q: “So, you synthesized this pitolisant and then used it as a comparator as part of your work on this class?”
A: “In pre-clinical, yes.”
Q: “And then, what did you observe? Did you observe the same issue with bioavailability?”
A: “Yes…they didn’t solve the problem, and we didn’t solve the problem as well.”
Q: “And how do you know that pitolisant has the same bioavailability problem? How did you test that?”
A: “In animals.”
Q: “And what was the availability that you observed? Do you remember for pitolisant?”
A: “The variability was very similar to our compound. I don’t remember the exact data anymore. Unfortunately, it’s been a couple of years. But the variability was very similar to our compound. “Again, we didn’t see much it passing the blood-brain barrier. I think the number, I remember it was around 3% to 4%, something in that range maximum, with very high variability.”
Q: “Wow. So, how does pitolisant even work then?”
A: “I mean, you have seen Takeda eliminating a narcolepsy program because of toxicity? It's an area where there are a lot of products failing one after another. That's called TAK-994, an orexin antagonist. That's another mechanism, but that failed miserably.” –Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Source: Scorpion Capital consultation calls with experts
He emphasized the severity of the drug development obstacles unique to H3 receptor compounds, which means that “you’ll never be able to take that product into a clinical program to bring a reasonable effect to the patient,” except by giving them an over-the-top toxic dose in the range of 30X the max dose on the pitolisant label, given the volume needed to overcome the “very, very low bioavailability.” He underscored the “huge patient-to-patient variability in terms of how it’s absorbed: “the biggest problem here is what we call DMPK, Drug Metabolism and Pharmacokinetics, the mechanism of action.” He added pitolisant is also doomed as “having the same problem” and that therefore “you will never see a significant effect, a reasonable and reproducible one.”

H3 receptor drugs as a class are doomed by “huge patient-to-patient variability,” lack of bioavailability, and blood-brain barrier issues

“The biggest problem of that molecule, the receptor, is interesting. The class is interesting. Narcolepsy is a huge need. Here is the problem. This product has a huge patient-to-patient variability in terms of how it’s absorbed and how it actually passes the blood-brain barrier or moves past the blood-brain barrier. So, the biggest problem here is what we call the DDMPK, Drug Distribution and Metabolism, the mechanism of action. In a lab, it works wonderfully. In cells, it works, even in rat models, and we’ve even done models in dogs, and it works. The problem is in humans, the metabolism of such drug classes allows very high variability and very, very low bio-availability to reach even a 1% maximum. And that’s why you’ll never be able to take that product into clinical program to bring a reasonable effect to the patient, except that you have to give patients something like 900 grams of the drug because the bio-availability is too low, and the variability is very high.”

– Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Lack of bioavailability and high variability are a class problem that also afflicts pitolisant

Q: “So, you were involved with the H3 inverse antagonist. And then, was it basically identical to pitolisant or was it a different H3 receptor than theirs? Does theirs have better availability? Or do you think theirs is also only 1% available?”

A: “Theirs is also having the same problem, all belonging to the H3-R inverse agonist kind of drug. And they are very simple, actually molecules, and they can have multiple indications. But the problem, if you don’t solve it, it’s basically that the bioavailability is extremely low. You will never see a significant effect, a reasonable and reproducible one.”

– Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company
The ex-Abbott scientist indicated Bioprojet has a “mediocre reputation”; that pitolisant’s problems are “really very typical for the same class”; and was dismissive of their clinical trials, attributing the minor ESS score reductions on the primary sleepiness endpoint to “a clear placebo effect, study bias, concomitant medications, and other flaws.

**Stated that Bioprojet has a “mediocre reputation”**
Q: “Pitolisant came out of this laboratory called Bioprojet in France. The person is Jean-Charles Schwartz, a French scientist who’s spent his entire life working on this mechanism of action. Do you know anything about them or their reputation?”
A: “Bioprojet, yeah, I know them.”
Q: “What is their reputation?”
A: **“Mediocre reputation.”** – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

**Pitolisant has various PK characteristics “very typical” for the class” regarding lack of bioavailability and brain penetration**
A: “If you have the label and you can take a look into the pharmacokinetics, the medium time to maximum plasma concentration is 3.5 hours. Serum protein binding is approximately 91% to 96%. The blood-to-plasma ratio is 0.55 to 0.85. **That is the problem. It degrades to a metabolite and then binds it completely to plasma. And then from there, you get very little that’s able to really pass through the brain.**”
Q: “The numbers that you just mentioned are the ones that you observed at Abbott?”
A: “Very similar unless you have different compounds, so it's not exact. But it's **really very typical for the same class.**” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

**Ex-Abbott scientist was critical of pitolisant studies, attributing the minor effect to placebo, study bias, etc.**
“You can see the differences between the placebo and EDS score is not much. The effect is very mediocre. You dropped off -2 to -3 in almost two months. That's not much. And you have seen already a placebo effect. **A clear placebo effect.** Like if you take a look from baseline, you dropped 2 ESS scores minus, actually, ESS score minus from baseline to 8 weeks on placebo. And then you have a delta of another -2 between the placebo and the active. Do you see what I'm trying to say? And that's not to be too hard with a drug. Also, these patients are normally, **as soon as you put them into care, they respond anyway.** But I think that just the effect of the drug is not clear enough for me, at least. And also, you don't see much of a clear separation between week 2 and up to week 8. You may be seeing something from baseline to week 1, but after week 1, **the separation test of the placebo is not increasing. It's just patients improving because they have a better follow-up in the study. They have better care in a study.** Because these patients are coming in, they have nurses taking care of them. Sometimes they get concomitant medication, concomitant psychology care, and so on. Overall, these patients are improving. It's not because of the drug that they are improving.” -Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company

Source: Scorpion Capital consultation calls with experts
The ex-Abbott scientist indicated the GSK program had “very similar problems” and has been “terminated completely,” based on his conversations with staff there. He stated that “their finding was very similar to our findings” regarding “the blood-brain barrier and how difficult it is.”

GSK apparently had a similar H3 receptor program with the same problems and now terminated
Q: “And what do you know about the GSK and the J&J H3 receptor programs?”
A: “GSK, I have been monitoring that product for a while, and it has very similar problems, and really, the last I hear from colleagues is that it has been terminated completely.”
Q: “Was it very similar to pitolisant and the one you were doing at Abbott?”
A: “Yes.”
Q: “Did you ever speak to somebody on the GSK program?”
A: “Yes, I have a couple of friends who were working on that one. It's a small world, specifically neurology.”
Q: “What did they tell you?”
A: “I think they, in general, and what we shared was the common methodology of testing and so on. And we had been discussing also passing the blood-brain barrier and how difficult it is. And I think my impression that their finding was very similar to our findings as well.” – Senior pharmaceutical executive/scientist, previously at Abbott and now at another major pharma company
We also consulted a longtime scientific leader at GSK, a major pharma company, who was involved in their extensive H3 receptor program. He corroborated the color from Abbott and J&J about the lack of efficacy and severe toxicity in the class: the “guys [you spoke to] from Abbott are correct...actually there was some discussion even between GSK and Abbott to collaborate” in the space. He stated that GSK developed and tested numerous antagonists/inverse agonists but that they quickly failed in phase 2 trials. He bluntly summarized the unsolvable dilemma, that at lower doses there is no bioavailability, but toxicity if you escalate the dose – “the problem starts with bioavailability but then the toxicity starts appearing after that.”

**Scientist spent >10 years at GSK; worked on an extensive H3 receptor program; failed immediately**

A: “That's right. I spent [redacted – more than 10] years at Glaxo.”

Q: “And you were involved in an H3 receptor program there?”

A: “Yeah, I was involved in the production of the ligands and also in the scientific and treatment strategy.”

Q: “How many different antagonists, inverse agonists for the H3 receptor did they try at Glaxo?”

A: “You're talking about the screening on the earlier research. I think I recall that we tried 3 agonists and 3 antagonists and 5 antagonists or even 6 antagonists during the selection period. And then after that, they progressed for early research with a couple of antagonists and a couple of agonistic mode of treatment, which, a couple of them failed during the first study.”

–Longtime scientific leader at GSK

**Concurred with Abbott’s findings on lack of efficacy and toxicity; no bioavailability at lower doses and toxic at higher ones**

Q: “I was talking to somebody that was at Abbott that was involved in their program and they said that the big problem they had was that there was just no bioavailability either in the animal studies or in the humans, that it was super variable, like up to 300% variability in bioavailability. That is like 1%, maybe 5% bioavailability. It was barely even getting into like the brain where the H3 receptors are mostly. So, they were like, the drug didn't work, it failed. The pharmacokinetics failed. What did you guys observe as far as bioavailability passing the blood-brain barrier? Obviously, there's no mechanism of action if it doesn't get into the brain.”

A: “Yeah, so these guys from Abbott are correct. Actually, there was some discussion even between GSK and Abbott to collaborate on that, by the way, for your info. I don't know if it was a successful thing or not. At the lower doses, the bioavailability it was all around, actually, all around the curve. And that's why some people tend to increase the dose to saturate the very systemic delivery of this medicine and in order to try to pass the blood-brain barrier and things like that. But then, we started seeing the side effects at certain doses. So, yes, the problem starts with bioavailability but then the toxicity starts appearing after that.”

–Longtime scientific leader at GSK

Source: Scorpion Capital consultation calls with experts
The scientist walked us through one phase 2 study in particular, at similar doses to the pitolisant trials. He stated it was “no good” on efficacy and “issues with the toxicity”: “there were some serious side effects when we tried to increase the dose.” He indicated that the toxicity was alarming enough that GSK’s governance committee quickly and prematurely terminated the trial after an interim reading, even though it had only enrolled 30-35 patients out of 100 planned.

**Failure due to toxicity and lack of efficacy; phase 2 prematurely halted**

Q: “And what happened — when did it fail and why?”
A: “It failed later, actually, at later stages. There are many why’s. It’s a kind of weird case but unfortunately, there was no good efficacy. And that was puzzling. When we attempted to increase the dose, there was some issues with the toxicity part.”

Q: “What were the toxicity issues? And these are all animal studies? Are these are healthy volunteer studies?”
A: “I’m talking to you about the animal studies and first time in humans and also phase 2 as well.

Q: “So, there was toxicity—where did you guys observe the toxicity in the animal and volunteers in the phase 2 studies?”
A: “Normally, we start with animals, as you probably know. And we do dose escalation in animals, so we did that, and it was fine up to the dose that we tried with animals. The first time in a human, as you probably know, they try a lower dose, which was fine. In the second study, phase 2, which again, this is toxicity but it’s a larger population you do what’s called dose escalation to try to see what’s the tolerability of the subject in terms of dosing, and what dose they can tolerate. And yeah, there were some serious side effects when we tried to increase the dose.”

Q: “Do you remember at what dose that happened?”
A: “We started from 25 mg, we tried 50 mg, 250 mg, 100 mg, something like that. That was one of the problems because it’s working with cellular signaling.”

Q: “This was the Alzheimer’s trial, GSK239512?”
A: “Yes, I think you are right.”

Q: “I’m just looking it up online while we’re talking. A 16-week, phase 2, multicenter, randomized, double-blind, placebo-controlled trial. Started November 2009. It was supposed to end a year later, in November 2010. Do you remember how many patients were enrolled?”
A: “Yes, that was actually phase 2 was less than 100, I think there were 30. I think we did around 30-35 patients for phase 2.”

— Longtime scientific leader at GSK
A significant percent of the 30-35 patients in the phase 2 experienced a variety of serious adverse side effects, such as liver toxicity, blurred vision, and vomiting: “there are hepatic changes…yeah, where were a few side effects actually….liver enzyme, a big interruption.” He stated that the side effects started at low, sub-therapeutic doses “even if it has no effect or it has no action,” suggesting that toxicity may be related to CYP3A4 metabolism in the liver or toxic metabolites.

**Significant percent of patients in phase 2 had serious adverse effects including blurred vision, liver changes, and vomiting**

Q: “Do you remember how many patients had adverse effects in phase 2?”
A: “I don’t remember the exact number but it was significant enough. If it’s clear and if it is even like two or three patients, that’s enough to kill that program. Especially, in phase 1, phase 2, because the total number of people is, as I said, in phase 2, is just 100 so when you see 3 or 4 people saying the same side effects, that’s already 5 percent, and the risk itself can be measured by the impacts of the risk. Itching or pain in the injection area or whatever, that’s fine. But when you talk about the neuroscience, neurology, sleeping, things like that, that can be high-impact risk.”

Q: “And you said there were some people that had blurred vision after taking the drug?”
A: “Yeah, there were many side effects like blurry eyes or blurry vision, vomiting, nausea. There are hepatic changes. Yeah, there were a few side effects, actually.”

Q: “You said there was vomiting, blurred vision, and you said hepatic change, like liver change?”
A: “Right.

Q: “Is that what you said?
A: “Yeah, the liver, exactly. The liver is more likely. Yeah, so there was some liver enzyme, a big interruption, changing and enzymes in the liver because of the detoxification enzyme.”

Q: “Wow, so you guys observed adverse effects that were neurological and hepatic. That’s pretty serious.”
A: “Yeah, that’s why it was killed, right?”

Q: “You said the dosages that were tried in phase 2, at what dosage did the side effects start? Was it at 25 or was it only at 50?”
A: “At 25, 50, I mean, they do start even at a very low dose, even if it has no effect or it has no action just to see the tolerability of the body for this kind of molecule. So, 25 and then 50 and then 100 and then 250 and then they go up.” —Longtime scientific leader at GSK

Source: Scorpion Capital consultation calls with experts
In addition to toxicity, the GSK scientist shared pharmacokinetic and bioavailability problems identical to the ex-Abbott scientist’s color, stating it never reached therapeutic concentrations in the blood and couldn’t sustain them even if it did. He echoed comments that it wasn’t “freely passing the blood-brain barrier,” and corroborated massive plasma variability and instability not only between patients but also within the same patient at different periods: “the bioavailability was fluctuating in both animals and humans”; “some mechanism of clearance for this drug”; “never reached” a “certain concentration.”

**Bioavailability was highly variable and unpredictable, even within the same patient at different times due to “mechanism of clearance for this drug”; never reached therapeutic concentration and/or sustained it; blood-brain barrier issues**

Q: “And what was the bioavailability problem that you observed?
A: “The bioavailability, I mean, the concentration in the brain was less than, around 3 [Inaudible 0:16:23] or less. And sometimes, when you take samples, and even in animals where unfortunately we take their brains and we measure the drug there. We realized that there are some low concentration in some samples and some of the samples, good concentration, and bioavailability in the brain tissue. So, we don’t know how the blood-brain barrier is actually interacting with the molecule. The bioavailability was fluctuating in both animals and humans.”

Q: “When you say fluctuating - some people had it, some people didn't? Or you just never knew if it was going to get in there or not?”
A: “Some people had more concentration, more bioavailability than others. And the same for the animal. Some subjects more than others, so that's what I mean by fluctuating among subjects. And also, within the same subject, when you take it at a different time period or when you measure it at a different time period, it's not sustaining the same bioavailability for a good time. You need some time for the drug to stay there in order to bind. So, sometimes, you measure, and you find a good concentration, and then all of a sudden, it's gone. There is some mechanism of clearance for this drug.”

Q: “So, you mentioned variability but do you remember what the actual level of bioavailability was? It was just not enough to be therapeutic, so you said you had to increase the dose, what was it? Like 1%, 3%? “
A: “Yeah-yeah, that's exactly what I mean. And we needed it to reach to a certain concentration. It never reached it, or if it reached it, it was not reaching it and sustaining it for a long time.”

Q: “And so, that's why you guys had to escalate the dose, and then you've got a toxicity problem.”
A: “Yeah, exactly. ”

Q: “Did you guys in the PK studies measure distribution in the brain, whether it crossed the blood-brain barrier? Any radiography?”
A: “Radio labeling - some people they do get the drug and we did that and that's what the bioavailability—it's kind of addressing the bioavailability point. And yeah, it was not that freely passing the blood-brain barrier just like with Abbott. So, that's why the bioavailability data was fluctuating.” —Longtime scientific leader at GSK
One of the most informative scientists we consulted spent decades at Johnson & Johnson/Janssen in senior neuroscience and other roles, with hundreds of published papers and patents to his credit. He was a pioneer in the field of H3 receptor drugs and published the foundational work - we found his name via his papers. He was as impressive as any scientist we have ever spoken to, with encyclopedic knowledge going back to the 1990’s of every player and compound in the H3 space. Critically, he had numerous interactions with Bioprojet’s founder Jean-Charles Schwartz and others at the lab. His knowledge of pitolisant and its flaws was in-depth – and devastating. As background, he indicated that Janssen (hereafter referred to by its parent J&J) was the leader in the H3 receptor space since the 1990s, publishing the first drug structures which Bioprojet, Pfizer, Merck, Glaxo, Abbott, Novo-Nordisk, and others then followed. He stated that they conducted “very robust trials” after screening countless compounds, across many indications such as narcolepsy – and that all of these efforts were failures.

*JNJ was the leader in H3 receptor space since 1999; one of earliest with published structures that others followed*

“We were the folks that actually cloned the human H3 receptor, and that's public domain, and we began with a high throughput screen. We ended up with a bunch of really good compounds, and once we published that stuff, every other company jumped on. Abbott was one of the early companies that definitively published structures; Pfizer, Glaxo, Merck, Novo-Nordisk, many, many companies became involved in H3 because it turned out it was relatively easy to find lead compounds...We began the program in 1999. ”—Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Conducted “very robust trials” across numerous indications that failed, including the same indications as pitolisant trials

“They were very robust trials. And in the public domain, there is a trial—I presented this, so I know it's in the public domain—we looked at excessive daytime sleepiness and narcolepsy. We looked at allergic rhinitis. We looked at ADHD. Pre-clinically—this is all published as well—we looked at alcohol addiction...and at the time, the decision was not to move forward, but that compound was called bavisant...So, they were looked at for the symptomatic treatment of Alzheimer's disease, they were looked at for excessive daytime sleepiness, for narcolepsy, and narcolepsy with cataplexy. We looked at it for allergic rhinitis... Yeah, we did the same—I'm looking at the results now. And this is public domain—it was presented in public. So, we looked at excessive daytime sleepiness in narcoleptics, and we compared it to modafinil, which is what Schwartz did as well.”—Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
The scientist was intimately familiar with Bioprojet’s history with pitolisant and was dismissive, stating they just appropriated a stale compound from someone else: “I don’t think those guys looked at tons of structures, to be honest. I think that’s a pretty old structure.” He stated that in contrast to J&J which tested hundreds of compounds, that Bioprojet “just stuck with the first compound that they got” – suggesting that Bioprojet didn’t even properly understand their own molecule vs. J&J which “did a hell a lot of chemistry around the templates we had.” He indicated that his team at J&J had independently developed compounds with the same molecular structure as pitolisant – defined by a piperidine ring – and viewed it as an inferior molecule.

JNJ looked at same molecular structures as pitolisant, with the same piperidine ring but with better chemistry; Bioprojet didn’t look at many structures; just borrowed from another academic and “stuck with the first compound they’ve got”; didn’t even seem to know its pharmacokinetics

A: "I don’t think those guys looked at tons of structures, to be honest. I think that’s a pretty old structure. My thought was that those structures—a lot of that stuff came from a guy called Robin Ganellin at University College London. And what he was looking for, it’s got a chlorophenyl group in it, is my recollection. There was a whole series of histamine H3 antagonists that came out of this big group, which was UCL, Free University of Berlin, and another, and they had admitted it was all base compounds. So, they started with histamine and their focus was to look for replacements for the imidazole ring. So that whole chlorophenyl-propoxy piece, I believe, was in an older H3 antagonist, which had an imidazole ring, so it was based on histamine. What they did is they looked, and they just simply replaced the imidazole ring with a heterocycle, which I recall was piperidine."

Q: “Yeah, it’s piperidine. But is there anything that the piperidine ring gives them that everybody else struggled with?”

A: “Yeah, we had a core piperidine in some of them. The key to what we did, which other people recognized afterwards, was what controls the length of time it stays in the body to a large extent is the basicity of the piperidine ring. And what we published was that if you lower the PKA, which is the degree of basicity of that nitrogen, you can control the pharmacokinetics. And that was the key to the molecule we had. We published all this. It’s in a paper. And that gave us the pharmacokinetic profile that we were looking for. We drove the basicity down. We did a hell of a lot of chemistry around the templates we had. And you could add that piperidine ring—it can be a bigger ring; it can’t be a smaller ring. So, I think they just stuck with the first compound they’ve got.” –Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience
He indicated that J&J’s H3 receptor compounds were far better than pitolisant, based on their testing: “I am familiar with the pitolisant structure”; “very simple compound”; “we had much better compounds based on physical property and drug-like properties than pitolisant. So, we pursued those.” He added that “for every company that got into this, the pharmacokinetics presented a challenge” – echoing the same color provided to us by the ex-Abbott scientist.

**JNJ compounds were better than pitolisant but “for every company that got into this, the pharmacokinetics presented a challenge”**

Q: “What did you mean by your statement that the compounds that you came up with were better than pitolisant?”
A: “We wanted compounds where we drove everything off target engagement. So, we wanted to know what exposure you needed to get target engagement centrally for activity. And we also wanted to understand the pharmacokinetics, and for every company that got into this, the pharmacokinetics presented a challenge. The pharmacokinetic behavior is how the body treats the drug. So, what you need for this type of drug is a compound with a relatively short half-life. That's because it's a pro-arousal; it keeps people awake. And we actually published and presented the data, whereas if your compound half-life is too long, you're going to keep people awake for days. And so, the concern is that you want a compound with a relatively short half-life that you can give once a day. And for every company, it was a challenge. So, we got fairly close to that; other companies got pretty close to that, that they could take the compounds in the clinic. But we also measured central engagement in the brain, and we did that with positron emission studies. We used a PET ligand in healthy volunteers to find out what dose do we have to give to get central occupancy for this receptor in the brain.” –Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

**JNJ was intimately familiar with pitolisant but had “much better compounds”**

“We were aware of pitolisant. It wasn't called pitolisant when we got into this. We had much better compounds based on physical property and drug-like properties than pitolisant. So, we pursued those. And we had compounds that were good enough to take into a number of clinical trials, which are in clinicaltrials.gov… So, I am familiar with the pitolisant structure. That actually came from a collaboration between Bioprojet and a bunch of European investigators, the Free University of Berlin, and the University College London. Very simple compound.” –Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
The scientist described interactions with Jean-Charles Schwartz that led him to conclude that Bioprojet were amateurs and lacked basic pharmacokinetic data about pitolisant, and noted that Schwartz “did seem to be concerned” when he learned of data that J&J had. He added that “its pretty damn clear to me that their pre-clinical stuff was no way near as robust.” In his opinion, Bioprojet was ignorant of basic information about their own compound: “I came away thinking, you know what? These guys haven't got that piece of information, which I think is necessary to progress the molecule.”

Schwartz lacked basic pharmacokinetic data about pitolisant and appeared to express concern; “pre-clinical stuff was no way near as robust”

Q: “Do you have any sense of what the half-life is of pitolisant just based on anything you read or whatever you heard kind of word of mouth at these meetings and so forth?”
A: “I honestly don't know, and like you, I've never seen the data. I got the impression when Jean-Charles spoke to me—and this is 10 years ago, probably—I presented data from our compounds and showed them how we could correlate target engagement and exposure in rodents, how we could go and translate that into exposure and target engagement in humans using PET. And then we had the half-life, obviously, in different species as well. And he seemed surprised that we had all that data. And I also had the impression—and it's an impression—that they had not thought of that. Because I said to him based on what you showed—I think I asked him about the half-life—and he did seem to be concerned…but it's pretty damn clear to me that their pre-clinical stuff was no way near as robust. The first compound that was made, the half-life was in rodents, and I published this—it was still in the brain after 96 hours. And other companies saw the same thing. Even the templates—all the templates are related to some extent. They have an aromatic portion, and they have a basic amine. I've published all this stuff.”

Schwartz was ignorant of basic pharmacokinetic data “necessary to progress the molecule”

Anyway, Jean-Charles Schwartz got up and spoke first, and he presented a—my recollection is a narcolepsy study. We had done a similar narcolepsy study which was in the public domain…but what we had done is looked at what the exposure was in the brain. That was a big concern because we didn't want anything hanging around. And he came up to me afterwards, and the only time he was nice to me and he asked me about the PET study. And I said we wanted to know what the pharmacological half-life was, and we didn't want compounds with a very long half-life with target engagement in the brain, central occupancy for a long period of time. Now, I can't remember this in as much detail as I could. But I came away thinking, you know what? These guys haven't got that piece of information, which I think is necessary to progress the molecule.”

Source: Scorpion Capital consultation calls with experts
He outlined red flags that undermine Bioprojet’s scientific claims: that they lacked the ability to test pitolisant properly against a human H3 receptor and were dependent on rodents; used “old-school pharmacology” and had no idea “how good it was against the human receptor”; “I don’t want to bad-mouth another scientist… but there were limitations on what Schwartz could do… in characterizing the compound”; “I’ve never seen data with respect to speciation… how does it perform against… mouse, rat, dog, or human?”

Doesn’t bind b/c of speciation issues; never tested it against the proper receptor; amateur hour: Schwartz used “old-school pharmacology” with rodents and lacked ability to test properly against the human H3 receptor

“The other thing I’ve never seen for that molecule is, well, is speciation. The reason we could move very, very fast is that we had the human cloned receptor. So, we could screen our compounds against the human receptor, whereas all the work done prior to that—and Abbott was quick to do this as well because they had actually cloned a receptor that mistakenly characterized it as a cholinergic receptor, not a histamine receptor […] But when Jean-Charles Schwartz did this, it was old-school pharmacology with, I guess, it was rodent tissue strips or something. Or it was in some sort of tissue. So, they used rats. So, all their compounds that they found initially were good for rats. And then they kept advancing the compound, but, of course, they hadn’t got access to the human clone, so they didn’t know how good it was against the human receptor. There was a Wakix screen against the human receptor, but it was really, really complex. And I remember talking to Sir James Black, who had found the H2 antagonist years ago, about what tissue do you use in humans. And I don’t know if anybody ever did, but I think it was a saphenous vein, which is the big vein in your leg. So, there are at least three receptors there, and you could do the tissue-type screening.”

Bioprojet compounds were for rats and lacking “data against the human receptor”; also off-target H4 receptor binding

“The point I’m making is they had great compounds for rats. I’d never seen data against the human receptor. They must have it somewhere. The other thing is some of those compounds, a year after [redacted] cloned the H3 receptor, he cloned the H4 receptor, so there’s a fourth histamine receptor. We characterized the histamine H4 receptor. And one of the first things we did was take all the H3 compounds that we had access to, to determine if they had an affinity for the H4 receptor. And a lot of the older histamine-based H3 receptor compounds, they have relatively high affinity for the H4 receptor. I’ve never seen that data for pitolisant. I think that’s less likely but for them to have H4 affinity, but I don’t know […] The other thing is I’ve never seen data with respect to speciation. So, how does it perform against, say, a mouse, rat, dog, or human? And we wanted to show our compounds were super-specific, and we knew they had an affinity for H3 in the mouse, so what we did is we made a knockout mouse that had no H3 receptors, and we showed that our compounds didn’t bind anywhere in these animals where there were no H3 receptors. So, we knew that our compounds were highly specific for the H3 receptors. All of this stuff is published. I don’t want to bad-mouth another scientist, but I would say there were limitations on what Schwartz could do in terms of characterizing the compound.” – Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
The most troubling color from the ex-J&J scientist concerned pitolisant’s cardiotoxicity. It appeared to us that he was in possession of damning information which he couldn’t share, which we speculate may have been based on potential licensing conversations 15-20 years ago: “There’s a piece of information. I know more than I’m telling you, but I can’t tell you everything”; “I knew they had cardiovascular issues”; “I don’t think it was a particularly good compound.” His comments led us to believe that other companies also evaluated pitolisant and were concerned about the toxicity: “That compound had issues. The main issue is it had a cardiovascular signal.” He added that the H3 compounds taken to clinic by other pharma companies were “much better in terms of drug-like qualities.”

Pitolisant “had cardiovascular issues”; “a red flag to people”; not a “good compound”

A: “I don’t think it was a particularly good compound, but you’ve got to give Jean-Charles credit for getting something on the market. Now, I also know Xavier Ligneau. I’ve had scientific interactions with him… I knew they had cardiovascular issues, and they actually did present in a meeting in Ireland how they solved those—and I was at that meeting—but I can’t recall what it was other than that they were able to actually launch it.”

Q: “And, by the way, I don’t think they’ve solved it because I’m starting to see these reports of cardiotoxicity that are starting to trickle out now.”

A: “I don’t know what it was. There’s a piece of information. I know more than I’m telling you, but I can’t tell you everything.”

Q: “Was it about a cardiac event or toxicity or something?”

A: “…I don’t know the details of what the cardiac situation was, but yeah, it was a red flag to people…”

–Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Pitolisant “had issues” and “the main issue is it had a cardiovascular signal”; others’ H3 compounds were “much better”

“That compound [pitolisant] had issues. The main issue is it had a cardiovascular signal...it was launched as Wakix, it was Jean-Charles Schwartz's baby. He was the one that actually identified the H3 receptor and showed where it was in the brain. And he did that before it had actually been cloned. It wasn't cloned; it was done by classical pharmacology. And my colleague [name redacted] cloned that receptor, which is why we started working on it. So, yes, you’re correct. There are many H3 antagonists out there. I would say the compounds from big pharma, which you’ve already named, they are much better in terms of drug-like qualities. They were taken into the clinic for many indications. You can find that all in clinicaltrials.gov. Years ago, I went through clinicaltrials.gov and made a chart.”

–Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
The scientist’s comments were cryptic and concerning: “Let me just give you a piece of...that’s not to say that other companies did look at pitolisant. And you’re correct. There is this cardiovascular signal, which was known - I’m sure it was known as soon as people profiled it.” As additional evidence, he stated that Lilly also observed cardiotoxicity in their H3 clinical trials but that it is not public: “they observed some things in clinical trials. They told me what they observed, which I don't believe is in the public domain.”

**Known cardiotoxicity signal; other companies “did look at pitolisant”**

Q: “So, there are two papers that I’ve come across where one person said that in their lab, we tested the hERG channel blocking for pitolisant, and they said it was off the charts, and they actually referenced the value. And they said this was confirmed by another lab, and they referenced a verbal conversation. They didn't footnote it; it wasn’t published. So, there are two citations that I’ve come across that are very brief and very vague that reference cardiotoxicity. And then there’s actually a paper that the Bioprojet people put out where they propose this algorithmic method for identifying hERG toxicity based on whatever the molecular structure is. But I thought it was very interesting that the paper was in 2011 after they’d already done a lot of work on pitolisant, and they called it BF2-something or the other or tiprolisant at the time. They never mentioned pitolisant, which made me realize that they seemed to know that it may not be as safe from a cardiac standpoint as they’re saying now because otherwise, they would have mentioned it in that paper.”

A: “Yeah, you’re probably right. I’m trying to think. Let me just give you a piece of...that’s not to say that other companies did look at pitolisant. And you’re correct. There is this cardiovascular signal, which was known—I’m sure it was known as soon as people profiled it. But I never ever had access to that data other than through conversations at meetings from other scientists...so, if we had been super, super interested, we could have done it in another country, but we weren’t because we felt we had much better compounds—**we knew we had better compounds.**” –Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

**Lilly and other companies also observed cardiotoxicity in H3 drug “clinical trials”**

“I've heard Lilly was also involved in H3. And I have heard that some companies, they observed some things in clinical trials. They told me what they observed, which I don't believe is in the public domain.” -Ex-longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
He hinted - in our opinion - that J&J could easily have licensed pitolisant if Bioprojet’s claims were true but ran for the hills: “if we had been super, super interested, we could have done it…but we weren't because we felt we had much better compounds - we knew we had better compounds”; “if we felt that was the bee’s knees....” He also expressed skepticism of pitolisant’s published hERG/cardiac safety study, calling the methodology old-school and primitive, and stated that he “would be surprised” if pitolisant “would get a passing grade” now on cardiovascular safety.

We speculate that JNJ evaluated licensing or buying pitolisant and ran for the hills
Q: “I don't even know if they’ve done those studies because when I tried to find any published PK studies from Bioprojet, there’s almost nothing out there.”
A: “To be honest, the fact that I can tell you—I can only tell you what I've seen [in public] at meetings. You can tell what the level of interest we had in that particular type of structure was. If we felt that was the bee's knees, and that was the way to go, I think it's possible if we wanted to get ahead of another company—”
Q: “You would have licensed it in a nanosecond, like any big pharma company.”
A: “Now you're touching on areas I can't talk about.” –Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

“Would be surprised” if pitolisant “would get a passing grade” now on CV safety; purported hERG assays are primitive
“When the compound was discovered, which we'll say in 2005. In those days, there had been a lot of drugs withdrawn from the market because of what they call Torsades de Pointes…when that happens, it's pretty quick you're going to die shortly afterwards. So, there are a number of compounds. Astemizole and Seldane, the antihistamine, and there were many others. There was a compound from Pfizer as well. They all saw what's called QT prolongation, and then they were able to associate that with the hERG channel. So, everybody then becomes concerned about, well, we have to have a hERG-binding screen in our drug-drug discovery efforts because we don't really want to launch a compound with all these problems. In the intervening years, hERG is a component—and they have high throughput patch plant methods now—so, your hERG component, your measurement is important. But with the advances in sort of molecular biology, you can now use cardiomyocytes, beating cardiomyocytes. And so, those assays have become just as important. So, hERG is now just one component of cardiovascular safety. What a company—and what I would do in my laboratory—we would have much more sophisticated cardiovascular safety. I would be surprised, based on what I've heard about pitolisant, if it would get a passing grade in what we would do, say, in 2022. So, there were a whole lot of changes happening between 2002 and now to make sure that the cardiovascular risk of your compounds is minimal or at least it's manageable.” -Ex-longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience
He expressed other criticism of pitolisant, stating that the compound was so old—dating back perhaps to 1999 or earlier—that it couldn’t have any intellectual property left. In addition, he was familiar with Harmony’s recent phase 2 data for sleepiness in Prader-Willi syndrome, and indicated it was anecdotal and lacked credibility: “there are far better H3 antagonists out there if this works. So, if an H3 antagonist works with Prader-Willi, then there are better compounds out there that are probably safer. I got the impression, too, a lot of pharmaceutical companies thought H3 was a target in search of a disease.”

No intellectual property as pitolisant is an ancient compound dating back to 1999 or earlier
A: “The other thing about that compound is I don’t know how strong the intellectual property is. I’m assuming you’ve looked at that.”
Q: “It’s one of the things I need to get to. But the thing is so old.”
A: “It’s got to be. My recollection is I saw applications from Jean-Charles Schwartz, from Walter Schnunack, and all these old guys—Walter is actually dead now—they had huge patent applications that they filed. But I don’t know—I’m not an attorney. I think that compound was out there in 1999. So, that’s a long time ago. So, if they got any patent life, I don’t think it can be very much.” —Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Prader Wills study is anecdotal and irrelevant; pharma companies dismissive of H3; “better compounds out there that are probably safer” than pitolisant
“I’ve seen clinical trial results geography-dependent. I did a meeting in Poland last month where I saw a presentation on Wakix. And Wakix has been picked up by—is being used by a charitable group in the United States that are focused on Prader-Willi Syndrome. My recollection, though, is that it was anecdotal data. They spoke to the patients, and I saw some videos of the patients, and they seemed better. But it was all anecdotal. I don’t think—I’m not sure the patient population is big enough for it to demonstrate a statistical significance, actually. But that’s where they’re going, and they got this charitable foundation, I think, to work with them. And I remember saying to the guy that presented, I said there are far better H3 antagonists out there if this works. So, if an H3 antagonist works with Prader-Willi, then there are better compounds out there that are probably safer. I got the impression, too, a lot of pharmaceutical companies thought H3 was a target in search of a disease.” —Longtime senior scientist at Johnson & Johnson, with global leadership roles in neuroscience

Source: Scorpion Capital consultation calls with experts
The early warning signs in Bioprojet’s pitolisant clinical development program
The danger signs with pitolisant started early. The first patient data was published in 2007, when the drug was still known as tiprolisant. Bioprojet conducted a phase 2 sequential two-week single arm study for EDS in narcoleptic patients – 22 adults, with a week of placebo then 40 mg/day for the second week. The first danger signal is that plasma levels were highly elevated and variable – a stark contrast to claims in later trials which conceal the risk given the drug’s CYP2D6 liability. Plasma levels after a week averaged 101 ng/ml – a level significantly higher than that listed in the FDA clinical review, based on trials that tried to downplay the hERG and QT prolongation risk. Moreover, the standard deviation was 78 ng/ml, indicating massive variability across patients. Five of the patients had plasma levels greater “>150 ng/ml.” The omission of pharmacokinetic tables is a striking red flag – and the paper used a crude trick by saying “greater than” versus stating how high the levels spiked, much less showing a distribution.

*Pitolisant pilot study, first published in 2007, indicates massive plasma level variability*

An inverse agonist of the histamine H₃ receptor improves wakefulness in narcolepsy: Studies in orexin⁻/- mice and patients

Tiprolisant dosages were performed at the end of the treatment period with a median sampling time at 3.75 h after the last drug intake. The plasma level average was 100.6±78.1 ng/ml \((n=17)\). Elevated plasma levels \( (>150 \text{ ng/ml}) \) were observed in 5 patients, in some cases related to the experience of adverse events occurring a few hours after drug intake.

Source: https://pubmed.ncbi.nlm.nih.gov/18295497/
We note another red flag in the 2007 pilot study – another statistical trick so cunning that it suggests Bioprojet went to great pains to conceal the danger of elevated plasma levels. The paper states that 5 of 22 patients had elevated plasma levels >150 ng/mL but doesn’t state how high it spiked. Yet the paper is written to convey the impression that the average plasma level and range is far lower: “the plasma level average 100.6 + 78.1 ng/mL (n=17).” But note the insertion of “n=17” – in other words, the study had 22 patients, but Bioprojet EXCLUDED the five with plasma levels >150 ng/mL in the calculation, making it impossible to deduce how high it went. In our opinion, the paper exemplifies what we believe to be a 20+ year pattern of scientific and clinical dishonesty by the inner circle that pop ups repeatedly in Bioprojet’s key papers and trials, all of whom are authors on the paper.

*Pitolisant pilot study, first published in 2007, indicates massive plasma level variability*

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Even with using the clearly fraudulent “plasma level average” in the paper, 1/3 of patients would exceed one standard deviation, meaning a significant percentage in the QT danger zone with plasma levels >179 ng/ml (101 ng/ml average + 78 ng/ml standard deviation) – with just one week of dosing. Patients within two standard deviations implies 257 ng/ml. These plasma levels indicate substantial risk of QT prolongation with no margin of safety. The FDA’s clinical review noted that “there was a clear and direct correlation of pitolisant exposure with QTc prolongation” and that “at supratherapeutic doses, QTc increases greater than 10 msec are anticipated” – 10 msec is typically viewed as the point where QTc liability is sufficient to prevent FDA approval. Even using Harmony/Bioprojet data which we think significantly understates the risk, plasma levels above 175 ng/ml are already at the danger threshold with ~10 msec QT prolongation; and >250 ng/ml is at a red-alert level.

**FDA CDER Clinical Pharmacology Review, Dec 2018**

The effect of pitolisant was evaluated in clinical studies P09-11 (TQT study) and P14-05 (SAD Study) and the agency performed independent analysis of these data (Darrts- IRT Report, Jose Vicente Ruiz et. al., 3/22/2019). The data analysis suggested that the highest therapeutic dose of 40 mg (salt form) at steady state did not cause any clinically significant QTc prolongation. However, there was a clear and direct correlation of pitolisant exposure with QTc prolongation. At supratherapeutic doses, QTc increases greater than 10 msec are anticipated. The detailed concentration QTc analysis are included in the IRT report.

**Table 6: The Point Estimates and the 90% CIs for ΔΔQTcF (ms) increases at therapeutic and supra-therapeutic dose levels**

<table>
<thead>
<tr>
<th>Safety Window</th>
<th>Cmax at steady state (ng/mL)</th>
<th>ΔΔQTcF (ms) &amp; 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest therapeutic Dose (i.e., 40 mg in salt form at steady state)</td>
<td>~73 ng/mL</td>
<td>4.2 (3.2, 5.2)</td>
</tr>
<tr>
<td>2.5-fold over highest therapeutic Dose</td>
<td>~175 ng/mL</td>
<td>9.8 (7.7, 11.8)</td>
</tr>
<tr>
<td>3.8-fold over highest therapeutic Dose</td>
<td>~280 ng/mL</td>
<td>15.5 (12, 18.9)</td>
</tr>
</tbody>
</table>

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf

**QTc prolongation of ~10 msec and ~16 msec at ~175 ng/mL and ~280 ng/ML, respectively**
The pilot study further contains a buried sentence that suggests an alarming risk of QT prolongation - as well as an attempt to conceal it. Given elevated and variable plasma levels, it’s not surprising the study noted seven severe adverse events across 22 pitolisant patients (32%) – using a dose similar to that on the current pitolisant label – with “six of them likely or very likely related to the tiprolisant treatment.” Near the end of the paper, it mentions “fainting sensation” as among the most severe adverse events. Tellingly, the distribution of severe adverse events listed in the relevant paragraph doesn’t mention fainting at all, but includes a vague category called “malaise sensation (n=2)” which we presume is an attempt to downplay the fainting – as fainting sensation (known as syncope) is well-established as the most common symptom of QT prolongation. Two patients with fainting across 22 total suggests an extreme cardiotoxicity signal.

*Pitolisant pilot study, first published in 2007, indicates high prevalence of significant adverse events*

First 3 days of treatment. Seven adverse events rated severe occurred in 6 patients during tiprolisant period (and two under the placebo period), six of them likely or very likely related to the tiprolisant treatment, i.e. insomnia (n=2), malaise sensation (n=2), nausea (n=1) and hallucination (n=1). None of these adverse events led to treatment cessation and 21/22 patients fully complied with the prescribed treatments. However, one patient reduced the dosage of tiprolisant from 40 mg/day to 10 mg/day because of adverse events such as mild auditory hallucinations without hypnagogic or hypnopompic characteristics, insomnia and malaise, which then disappeared with the dose reduction and another patient stopped the treatment the day before the exit visit with the investigator. Finally, there were no differences among placebo and period (31.8%). The most frequent adverse events were headache, nausea, insomnia, experienced mainly during the first 3 days of treatment. The most severe adverse events, i.e. insomnia and fainting sensation, probably related to an overdose of tiprolisant, given here in fixed dosage, could be substantially reduced, in future studies, by using an individual titration regimen and starting with a low dose of the drug.

Source: https://pubmed.ncbi.nlm.nih.gov/18295497/
Bioprojet appears to have quickly realized the toxicity risk at 40 mg – again, similar to the current dose on the label - as the next studies then tested 10 and 20 mg, and then took it down further to test 5 mg. Given that the trials with higher doses were flops with all manner of junk statistical and other tricks, as we detail in a later section, the sudden dose reduction dose is telling as companies typically try higher doses to elicit a therapeutic response. Bioprojet has run pitolisant trials for every indication under the sun, with no success, and we note that a number of later trials capped the maximum dose at 20 mg.

<table>
<thead>
<tr>
<th>Study start/end per ClinicalTrials.gov</th>
<th>Study title and indication</th>
<th>Dosages tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2010</td>
<td>Efficacy and Safety Study of BF2.649 in the Treatment of Excessive Daytime Sleepiness in Narcolepsy (Harmony1)</td>
<td>10, 20, 40 mg</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01067222?term=pitolisant&amp;draw=3&amp;rank=2">link</a></td>
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<tr>
<td>2010-2012</td>
<td>Effects of BF2.649 in the Treatment of Excessive Daytime Sleepiness in Narcolepsy (Harmony1bis)</td>
<td>10, 20 mg</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01638403?term=harmony+1bis&amp;draw=2&amp;rank=1">link</a></td>
<td></td>
</tr>
<tr>
<td>2010-2012</td>
<td>Efficacy and Safety of BF2.649 in Excessive Daytime Sleepiness (EDS) in Parkinson’s Disease (HARPS2)</td>
<td>5, 10, 20 mg</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01066442?term=bf2.649&amp;draw=3&amp;rank=2">link</a></td>
<td></td>
</tr>
<tr>
<td>2008-2011</td>
<td>Study to Demonstrate Cognitive Enhancing Effects of BF2.649 – Schizophrenia</td>
<td>“up to 20 mg per day”</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT00690274?term=bf2.649&amp;draw=3&amp;rank=4">link</a></td>
<td></td>
</tr>
<tr>
<td>2011-2014</td>
<td>BF2.649 in Patients With OSA and Treated by CPAP But Still Complaining of EDS (HAROSA1)</td>
<td>5, 10, 20 mg</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01071876?term=bf2.649&amp;draw=2&amp;rank=10">link</a></td>
<td></td>
</tr>
<tr>
<td>2011-2014</td>
<td>BF2.649 in Patients With OSA, Still Complaining of EDS and Refusing to be Treated by CPAP. (HAROSA2)</td>
<td>“up to 20 mg per day”</td>
</tr>
<tr>
<td></td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01072968?term=bf2.649&amp;draw=2&amp;rank=9">link</a></td>
<td></td>
</tr>
</tbody>
</table>
In addition to slashing the dose in later studies, Bioprojet’s pivotal phase 3 trials for pitolisant – now known as Harmony 1 and Harmony CTP - made another revealing decision: excluding patients with “serious cardiovascular disorder,” which is never defined. The long-term (12 mo) open-label Harmony 3 trial applied the same exclusion criteria. As we shall detail, narcolepsy patients exhibit numerous comorbidities, particularly obesity and cardiovascular issues. No cardiovascular exclusion criteria is listed in the pilot study, and we believe that the decision to then exclude such patients is an admission of the cardiotoxicity signal in the pilot study – as well as a reckless attempt to cherry-pick patients not reflective of a real-world clinical setting.

**Harmony 1 pivotal phase 3 trial paper**

Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial control method. Exclusion criteria were the use of any investigational drug within 30 days before screening, any other disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with sleep apnoea index ≥10 per h, an apnoea or hypopnoea index of ≥15 per h, or a periodic limb movement disorder with arousal index of ≥10), a history of substance abuse, a serious cardiovascular disorder, hepatic or renal abnormalities, or a psychiatric disorder.

**Harmony CTP pivotal phase 3 trial paper**

Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial

Exclusion criteria were participation in another trial within the month preceding screening, any other disorder with excessive daytime sleepiness (eg, sleep-related breathing disorder with apnoea index ≥10 events per h, apnoea–hypopnoea index ≥15 events per h of sleep, or periodic limb movement disorder with microarousal index ≥10 events per h), history of substance misuse, a serious cardiovascular disorder, severe hepatic or renal abnormalities, or a psychiatric disorder. Women of

Not surprisingly, Bioprojet’s narcolepsy studies fail to disclose cardiovascular safety data. Given that their preclinical papers, such as the *in vitro* hERG and Purkinje fibre study, asserted zero risk, the failure to showcase this safety profile with clinical data is damning. The Harmony 1 pivotal trial didn’t even conduct ECG’s on treatment groups — just a baseline ECG, presumably to cherry-pick and screen out patients with cardiac issues. The Harmony 1 paper states that “blood chemistry tests or hematological or cardiovascular parameters did not change in the three study groups (data not shown).” The Harmony CTP trial conducted ECG’s at each visit, yet once again no data or discussion is included other than the same sentence above from Harmony 1. The Harmony 3 paper states that ECG’s were conducted at baseline and at 6 and 12 months of dosing, but once again the data is missing and we are left with a single sentence asserting safety.

*Only a single sentence on cardiovascular safety in the papers for the pivotal phase 3 narcolepsy trials, with no data shown*

**Harmony 1**

Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial

three patients in the modafinil group. Blood chemistry tests or haematological or cardiovascular parameters did not change in the three study group (data not shown).

**Harmony CTP**

Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial

Blood chemistry and haematological or cardiovascular parameters did not change in either group.

Despite Bioprojet’s failure to show cardiovascular data in its narcolepsy trials, we uncovered worrisome QTc data in two pitolisant trials for a different indication – the only trials where we could locate a few crumbs. The trails were named HAROSA 1 and HAROSA 2, both for excessive daytime sleepiness in patients with obstructive sleep apnea (OSA). Neither trial appears to have been submitted to or reviewed by the FDA or EMA as part of their pitolisant approvals. The trials indicate a troubling QTc prolongation signal as well as fatalities. We emphasize that this is in spite of 1) using only a 20 mg dose – half the max dose on the pitolisant label; and 2) once again excluding patients with cardiovascular issues – indicating the significant real-world danger when the dose is doubled and patients are not cherry-picked. We begin with HAROSA 1, which was conducted from 2011 to 2014.

**HAROSA 1 publication - excerpt**

*Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP*

**A Randomized Trial**

**RESEARCH QUESTION:** Is pitolisant effective and safe for reducing daytime sleepiness in individuals with moderate to severe OSA adhering to CPAP treatment but experiencing residual EDS?

**STUDY DESIGN AND METHODS:** In a multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial, pitolisant was titrated individually at up to 20 mg/day and taken over 12 weeks. The primary end point was change in the Epworth Sleepiness Scale (ESS) score in the intention-to-treat population. Key secondary end points were maintenance of wakefulness assessed by the Oxford Sleep Resistance Test, Clinical Global Impressions scale of severity, the patient’s global opinion, EuroQoL quality-of-life questionnaire score, Pichot fatigue questionnaire score, and safety.

**RESULTS:** Two hundred forty-four OSA participants (82.8% men; mean age, 53.1 years; mean Apnea Hypopnea Index with CPAP, 4.2/h; baseline ESS score, 14.7) were randomized to pitolisant (n = 183) or placebo (n = 61). ESS significantly decreased with pitolisant compared with placebo (−2.6; 95% CI, −3.9 to −1.4; P < .001), and the rate of responders to

Source: [https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2820%2935105-9](https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2820%2935105-9)
The abstract for HAROSA 1 claims that “no cardiovascular or other significant safety concerns were reported.” However, the results section states that four patients in the pitolisant group (n=183) exhibited “at least one postdose QT interval” of >450 msec and that six patients “demonstrated one QTcF elongation of ≥60 msec.” The paper then downplays the issue by stating that two patients in the placebo group (n=61) also had a QT interval >450 msec and that three had an elongation ≥60 msec – which we find odd given the cardiovascular exclusion criteria. Several omissions suggest that the placebo comparison is a contrived attempt to muddy the waters. First, it says “>450 msec” and “≥60 msec” without providing the range or individual values – a classic case of “How To Lie With Statistics.” Did the pitolisant QT intervals spike far higher than with placebo? Second, how many postdose QT intervals >450 msec did the four patients exhibit? Stating that it was “at least one” is flagrant obfuscation.

HAROSA 1 publication – excerpt from safety discussion

comparable in the two treatment groups. However, in the pitolisant group, four participants (2.2%) demonstrated at least one postdose QT interval (using Fredericia's correction) (QTcF) of > 450 msec and six patients (3.3%) demonstrated one QTcF elongation of ≥60 msec, whereas two participants (3.3%) demonstrated QTcF of > 450 msec and three participants (4.9%) demonstrated QTcF elongation of ≥ 60 msec in the placebo group.
We note other obfuscations. The pitolisant QT interval spike is characterized as “postdose,” but the paper fails to state when the placebo interval >450 msec occurred. QT measurements are variable over the course of a day, and up to 470 msec is considered normal for females, making it straightforward to find a few point measurements for a placebo comparison within the vague parameters provided. Furthermore, data are shown for all adverse events in the tables *except* for QTc/QTcF - baseline values, range, and standard deviations are shown for all safety endpoints but are curiously missing for QT. The discussion states that “mean values of ECG variables were comparable in the two treatment groups” – another red flag, as the study was designed to specifically compare endpoints from baseline to treatment, not pitolisant to placebo. Picking and choosing after the fact is unacceptable. Baseline comparisons are not disclosed for ECG results as for other safety parameters.

**HAROSA 1 publication – safety tables curiously omit ECG and QT data, while including it for other safety endpoints**

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Safety Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Placebo (n = 15)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>86 (44.7)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>49 (26.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Leading to study drug withdrawn</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
</tr>
<tr>
<td>Baseline (V2)</td>
<td>129 ± 12.9</td>
</tr>
<tr>
<td>Range</td>
<td>100 to 180</td>
</tr>
<tr>
<td>End of D/B-treatment (V6)</td>
<td>128.7 ± 12.0</td>
</tr>
<tr>
<td>Range</td>
<td>78 to 157</td>
</tr>
<tr>
<td>Change (SD)</td>
<td>-0.6 ± 10.1</td>
</tr>
<tr>
<td>Range</td>
<td>-50 to 25</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
</tr>
<tr>
<td>Baseline (V2)</td>
<td>80.3 ± 8.9</td>
</tr>
<tr>
<td>Range</td>
<td>56 to 100</td>
</tr>
<tr>
<td>End of D/B-treatment (V6)</td>
<td>79.3 ± 8.9</td>
</tr>
<tr>
<td>Range</td>
<td>52 to 105</td>
</tr>
<tr>
<td>Change (SD)</td>
<td>-0.4 ± 7.3</td>
</tr>
<tr>
<td>Range</td>
<td>-25 to 29</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
</tr>
<tr>
<td>Baseline (V2)</td>
<td>70.9 ± 11.9</td>
</tr>
<tr>
<td>Range</td>
<td>40 to 107</td>
</tr>
<tr>
<td>End of D/B-treatment (V6)</td>
<td>76.6 ± 11.5</td>
</tr>
<tr>
<td>Range</td>
<td>43 to 115</td>
</tr>
<tr>
<td>Change (SD)</td>
<td>-0.9 ± 9.6</td>
</tr>
<tr>
<td>Range</td>
<td>-25 to 29</td>
</tr>
</tbody>
</table>

Source: https://journal.chestnet.org/action/showPdf?pii=S0012-3692(20)35105-9

114
HAROSA 2 exhibited an even more troubling cardiotoxicity signal, including a fatality – also conducted at half the maximal dose and again excluding patients with significant cardiovascular histories. The abstract states “no cardiovascular or other significant safety concern,” yet three patients on pitolisant had at least one prolonged QT interval >450 msec and 4 patients had at least one QTc longer than 60 msec - and one patient in the pitolisant group died due to cardiopulmonary failure (heart attack) - with only one patient in the placebo group experiencing QTcF >450 in placebo, no placebo patients experiencing QTcF >60 msec and no deaths in the placebo group. And again the same red flag - the investigators compare placebo to treatment at the end of study and do not disclose baseline to treatment changes in these patients.

*HAROSA 2 publication - excerpt*

Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment
A Randomized Trial

groups. However, in the pitolisant treatment group, three patients (1.5%) had at least one postdose corrected QT interval by Fredericia’s corrected QT interval (QTcF) longer than 450 ms, and four patients (2.0%) had one QTcF elongation greater than or equal to 60 ms, whereas there was one patient with QTcF longer than 450 ms in the placebo group.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193861/
Furthermore, the authors summarize the cardiovascular results in Harosa 2 by saying that “No key changes were found in...ECG test results...the changes reported in QTc (QTcF >450 ms and elongation >60 msec) did not differ significantly between pitolisant and placebo.” However, there were 7 patients total with QTcF prolonged greater than 60 msec (combining >60 with >450) vs. only one in placebo. The authors state that the death (heart attack) and QTc changes were not likely related to study drug but no explanation is provided for this assessment – and we emphasize that patients with significant cardiovascular disease were excluded from the study. In addition, the discussion states that in previous narcolepsy trials, patients “did not show any significant increase QTc” – but do not make a similar statement for this trial, because they once again fail to compare baseline to treatment. There is no reason narcolepsy vs. sleep apnea patients in HAROSA 1 and 2 would metabolize pitolisant differently.

Fatality in HAROSA 2 due to heart attack

TEAEs leading to study drug withdrawal were reported for three patients (1.5%) in the pitolisant group and two patients (3.0%) in the placebo group. Serious TEAEs were reported for two patients (1.0%; one prolonged QT interval on the ECG and one cardiopulmonary failure leading to death) during pitolisant treatment and considered unlikely to be treatment related and in none of the patients receiving placebo.

The paper falsely claims no significant difference in QTc between pitolisant and placebo

Our results confirm the favorable safety profile of pitolisant already reported in patients with narcolepsy (14, 15). No key changes were found in physical examination parameters or vital signs, depressive symptoms, and ECG or laboratory test results during the study. The changes reported in QTc (QTcF, >450 ms and elongation >60 ms) did not differ significantly between pitolisant and placebo. The pitolisant to placebo subject period. Accordingly, results reported with pitolisant in the previous randomized controlled trials in patients with narcolepsy (14, 15) did not show any significant increase in QTc. A recent 1-year open-label

Paper states no significant QT increase – but only for previous narcolepsy trials

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193861/
A PK failure that never should have made it past phase 1 – underestimated plasma levels are key driver of risk
We believe Harmony and Bioprojet have engaged in a systematic effort to conceal and under-estimate pitolisant’s plasma levels, which the evidence indicates are substantially higher and more variable than claimed and hence pose risk of toxicity. Pitolisant’s purported safety profile hinges on plasma levels not exceeding certain thresholds, as evident in the dose and titration guidelines on the label which exhibit concern of adverse effects. The max dose is 35.6 mg/day, but half that in patients with hepatic or renal impairment or poor metabolizers of CYP2D6. Moreover, the FDA’s clinical review noted that “there was a clear and direct correlation of pitolisant exposure with QTc prolongation and that “at supratherapeutic doses, QTc increases greater than 10 msec are anticipated.” The label states that at the max 35.6 mg dose, the steady-state C-max is 73 ng/mL with a range of 49.2 to 126 ng/mL. The CDER Clinical Pharmacology Review states the steady-state level is based on an undisclosed “Harmony model” – a black box.

Wakix label and excerpt below from CDER review

12.3 Pharmacokinetics

Following oral administration of pitolisant 35.6 mg once daily, the steady state C_max and AUC are 73 ng/mL (range: 49.2 to 126 ng/mL) and 812 ng*hr/mL (range: 518 to 1468 ng*hr/mL), respectively. Pitolisant exposure (C_max and AUC) increases proportionally with dose and steady state is reached by day 7.

<table>
<thead>
<tr>
<th>Drug exposure at steady state following the therapeutic dosing regimen</th>
<th>The population PK model (developed by sponsor with data from multiple PK studies) demonstrated mean exposures at therapeutic dose of 35.6 mg at steady state levels as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Mean Cmax = ~73 ng/mL</td>
</tr>
<tr>
<td></td>
<td>- Mean AUC = 812 ng*hr/mL</td>
</tr>
<tr>
<td></td>
<td>The exposures in CYP2D6 PMs were approximately 2-fold higher.</td>
</tr>
</tbody>
</table>

The FDA’s various pre-approval reviews indicate the agency simply accepted the company’s PK claims at face value, despite striking red flags that we shall detail. However, the European Medicines Agency, as part of their review in 2015, exhibited significant concern, noting “shortcomings in the documentation provided on the pharmacokinetics of pitolisant”; “many discrepancies”; “gaps in the understanding of the pharmacokinetics of the drug, introducing uncertainty…in the safety and efficacy…when administered to different subgroups or when co-administered” – “despite further analysis” requested by the EMA; and that PK in elderly patients or those with “renal and hepatic impairment could not be safely predicted.” The EMA therefore requested various PK studies as post-approval measures. We find one sentence particularly striking – that the “gaps include basic pharmacokinetic properties of pitolisant.”

*Pitolisant review by EMA’s Committee for Medicinal Products for Human Use (CHMP)*

The CHMP identified several shortcomings in the documentation provided on the pharmacokinetics of pitolisant. There were many discrepancies between the values of PK parameters in the different studies reports. Despite further analysis of the available data provided by the Applicant, there still are gaps in the understanding of the pharmacokinetics of the drug, introducing uncertainty in the assessment of the safety and efficacy of the product when administered to different subgroups or when co-administered with other drugs. These gaps include basic pharmacokinetic properties of pitolisant. Major elimination pathways are insufficiency understood for the drug and require additional investigations. Therefore, the Applicant has been requested to perform a new balance study after repeated dose administration in order to identify the major metabolites and characterize their PK behaviour and the mechanisms underlying their formation. This study will be conducted as a post-approval measure.

Common sense indicates that the “gaps” the EMA mentions in “the basic pharmacokinetic properties of pitolisant” are not accidental. Data this basic is only withheld if it is damning. There is zero chance, in our opinion, that Bioprojet and/or Harmony are not in possession of this PK information. It is always collected, particularly given Bioprojet’s prolific papers and trials over a multi-decade effort to conjure up a successful H3R drug. As part of our investigation, we engaged a consultant who specializes in pharmacokinetic analysis, who echoed the EMA’s comments and expressed shock at the lack of basic PK data across pitolisant papers and studies. The consultant stated that this was the first time in decades she could not locate published plasma concentration curves for an approved drug, even from animal studies much less humans: “I don’t know how Harmony got away with this, honestly”; “the lack of data in this regard is a huge red flag given that 2D6 is the primary p450 involved in the elimination of pitolisant”; “it is hard to believe it was approved without it.”

PK expert we engaged expressed shock at lack of pharmacokinetic data for pitolisant

“There are no plasma concentration curves to actually compare it meaningfully to preclinical data. I have never seen this before when researching any approved clinical agent. One can find bazillions of plasma curves. Why did they not measure plasma levels in their trials - say 1 week after stable dose initiation at Tmax/3 hr when steady state? Why are there no published PK curves even for the animal studies? Especially with the weird subjective stable dose selection criteria used routinely in these trials and now in patients? We don’t know what the peak plasma levels are and I do not take anybody’s word - show me the data. They say 75 ng/mL is the max level like that is a stable number – it is not. The lack of data in this regard is a huge red flag given that 2D6 is the primary p450 involved in the elimination of pitolisant – it’s hard to believe it was approved without this.”
The pharmacokinetics consultant expressed concern that actual peak plasma levels are unknown, and that Harmony’s hERG/cardiac safety claims “are quite meaningless without key peak and AUC information across patients.” She stated a 2D6-metabolized drug like pitolisant can exhibit “variation in exposures peak and AUC” of “20 to 40 fold.” She added that “plasma levels are very important with 2D6/hERG” and that Harmony’s cardiotoxicity-related assertions are useless if one does not “go way up in dose and correlate QT with plasma levels (peak and AUC exposures).”

PK expert indicated Harmony’s claims of cardiac safety are meaningless without relevant pharmacokinetic parameters

“So all of these careful and rather elegant in vitro/ex vivo and animal model studies for hERG are quite meaningless without key peak and AUC information across patients. I don’t know how they got away with this honestly. I was at the FDA and if I had seen these studies I would have insisted on plasma levels and perhaps additionally 2D6 phenotyping of patients in the studies. Variation in exposures peak and AUC can vary 20 to 40 FOLD for 2D6-metabolized drugs. That is something they wanted not to highlight - my guess. Also, one cannot easily measure QT prolongation close to baseline because it is so variable in a single individual over time unpredictably. It changes when you eat, when you wake up, when you stand or sit. It is all over the place so one must go way up in dose and correlate QT with plasma levels (peak and AUC exposures) then back calculate. In my experience, it is very linear when done that way, to determine/extrapolate the concentration where no effect would be expected. That is the safe plasma level. That was not done, or not reported in any review I have read including the 300 pages of FDA summaries you shared. Plasma levels are very important with 2D6/HERG.”

Source: Pharmacokinetic analysis commissioned by Scorpion Capital
Given the lack of typical PK data, the asserted plasma levels are suspicious and exhibit various red flags. For example, the label states that at the max dose of 35.6 mg/day, the mean plasma is 73 ng/mL with a range between 42.9 ng/mL and 126 ng/mL. However, the 2007 pilot study indicated it was 101 ng/mL with a standard deviation of 78 ng/mL – 38% higher with a wider range, despite the dose (40mg) being only 12% higher. Moreover, this pilot indicated 5 of 22 patients had far higher levels “> 150 ng/mL” – and as we noted earlier, the paper cleverly excluded those 5 in calculating the average of 101 ng/mL. This clearly indicates that plasma levels are significantly higher than the range indicated on the label, and that the label is a fiction.

*Pitolisant label indicates steady state Cmax 78 ng/mL (“range 49.2 ng/mL to 126 ng/mL”).*

12.3 Pharmacokinetics

Following oral administration of pitolisant 35.6 mg once daily, the steady state C<sub>max</sub> and AUC are 73 ng/mL (range: 49.2 to 126 ng/mL) and 812 ng*hr/mL (range: 518 to 1468 ng*hr/mL), respectively. Pitolisant exposure (C<sub>max</sub> and AUC) increases proportionally with dose and steady state is reached by day 7.

*2007 pilot study indicates 101 ng/mL with more variability, as well as a significant percentage of patients with levels elevated >150 ng/mL, who were excluded in calculating the average*

Tiprolisant dosages were performed at the end of the treatment period with a median sampling time at 3.75 h after the last drug intake. The plasma level average was 100.6±78.1 ng/ml (n=17). Elevated plasma levels (>150 ng/ml) were observed in 5 patients, in some cases related to the experience of adverse events occurring a few hours after drug intake.

The PK data and plasma level games continued with yet another study. The company submitted two cardiac safety studies to the FDA (“P09-11 and P14-05”) – both absurd, as we shall show. Neither study appears to be published, but we located a 2015 paper that excerpted some data from each. A table shows that the P09-11 study, conducted in 2010, tested a single 40mg dose of pitolisant in 25 males. The mean plasma level this time was 53 ng/mL with a standard deviation of 27 ng/mL. As this was a single dose, the steady state level after 7 days (with an accumulation ratio 2.3) is 122 ng/mL +/- 54 ng/mL, far higher than both the 73 ng/mL on the label and the 101 ng/mL in the 2007 pilot study – and indicates patients with 230 ng/mL and 284 ng/mL within two and three standard deviations.

2015 paper indicates even higher plasma levels than prior papers and label – table excerpt

Can an early phase clinical pharmacology study replace a thorough QT study? Experience with a novel H₃-receptor antagonist/inverse agonist

Table 2  Pitolisant pharmacokinetic parameters in the male subjects in the two studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TQT study (P09-11)</th>
<th>SAD study (P14-05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>40 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>240 mg</td>
<td>240 mg</td>
</tr>
<tr>
<td>Mean ± SD (CV)</td>
<td>52.88 ± 26.82</td>
<td>164.27 ± 62.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177.18 ± 48.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>229.02 ± 54.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>281.63 ± 46.79</td>
</tr>
</tbody>
</table>

Source: https://pubmed.ncbi.nlm.nih.gov/26879827/
As even more evidence that the asserted plasma levels are underestimated, we note a 2011 PK study (P11-3) of pitolisant in conjunction with a CYP2D6 inhibitor called paroxetine, in order to assess the effect of drug-drug interactions. The study is buried in the appendix of an FDA review document. Eighteen healthy adult males were given a single 20mg dose of pitolisant on two occasions, once alone and once concomitant with paroxetine (14 days later). The plasma level after the single dose (before paroxetine) was 28.40. At the labeled 35.6mg dose, this means 51 ng/mL. As this was a single dose, steady-state concentration after a week would be 102 ng/mL +/- 56 ng/mL, once again indicating that plasma levels of 214 ng/mL and 271 ng/mL within two and three standard deviations.

2011 PK study with paroxetine – table excerpt, p67

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf
In addition to steady-state plasma levels in the a) 2007 pilot study, b) the 2010 cardiac study, and c) the paroxetine study—all of which show levels far higher than the label—we located a fourth paper with telling crumbs of data. A 2019 paper for a small open-label, single-dose study in children and adolescents with narcolepsy stated that twenty-four patients were dosed at 17.8 mg—half the max dose. Data is shown for two subgroups—12 patients age 6 to <12, and 12 from age 12 to <18. Data is also shown for a comparator group of 13 adults (age 18-40), who were not part of the study with a footnote indicating “historical comparison group (data on file).” As we noted, Harmony and Bioprojet’s failure to publish proper PK data is damning, as it is inconceivable that they don’t have the data—and the footnote confirms the obvious.

Data table from 2019 PK study for pediatric narcolepsy patients

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacokinetic profile of pitolisant and its major phase 1 inactive metabolite.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Subgroup I</th>
<th>Subgroup II</th>
<th>Young adults&lt;br&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 to &lt;12 y</td>
<td>12 to &lt;18 y</td>
<td>18 to &lt;45 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 12)</td>
<td>(n = 12)</td>
<td>(n = 13)</td>
<td></td>
</tr>
<tr>
<td>Pitolisant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>55.5 (26.5)</td>
<td>36.5 (19.6)</td>
<td>17.8 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>47.2 (20.5–99.8)</td>
<td>29.1 (14.3–80.5)</td>
<td>14.2 (4.0–35.3)</td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>48%</td>
<td>54%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>50.0</td>
<td>32.3</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, Median (range), h</td>
<td>2.5 (1.0–6.0)</td>
<td>2.00 (1.0–3.0)</td>
<td>2.00 (1.5–6.0)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–10h&lt;/sub&gt;, ng·h/mL</td>
<td>316.1 (151.8)</td>
<td>182.2 (92.5)</td>
<td>94.2 (55.9)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>257.8</td>
<td>154.4</td>
<td>77.6</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>(112.8–611.9)</td>
<td>(81.6–386.9)</td>
<td>(22.3–229.4)</td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>48%</td>
<td>51%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>285.2</td>
<td>162.3</td>
<td>78.2</td>
<td></td>
</tr>
</tbody>
</table>

Footnote b indicates the obvious—Bioprojet is sitting on critical PK data that it has withheld.

Historical comparison group (data on file).
The table provides some clues to why they have not been forthcoming with proper PK data, as it shows dramatic plasma variability from patient to patient within each subgroup - orders of magnitude greater than the tight range on the label, and indicating serious risk of patients blowing past the safety margins at which hERG/QT and other toxicity can manifest. For example, within the adult subgroup, plasma levels ranged from 4.0 to 35.3 ng/mL, and from 14.3 to 80.5 ng/mL for 12-18 year old’s. We emphasize that this variability is apparent even within a tiny sample (n=12 or 13 patients), and after a single dose that is only half the max dose on the label, creating potential for even more variability in a real-world setting - demonstrating the EMA’s concern that the “basic pharmacokinetic properties of pitolisant” are unknown. We further note another red flag: patients were fed 30 to 60 minutes after the dose instead of being fasted, which means the actual plasma level is 25% higher or more, per typical PK parameters.

2019 PK study for pediatric narcolepsy patients shows massive plasma variability

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacokinetic profile of pitolisant and its major phase 1 inactive metabolite.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroup I</td>
</tr>
<tr>
<td></td>
<td>6 to &lt;12 y</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Pitolisant C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>55.5 (26.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>47.2 (20.5–99.8)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>48%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>50.0</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, Median (range), h</td>
<td>2.5 (1.0–6.0)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–10h&lt;/sub&gt;, ng·h/mL</td>
<td>316.1 (151.8)</td>
</tr>
<tr>
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<td>48%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>285.2</td>
</tr>
</tbody>
</table>

Cardiac safety data submitted to the FDA was a sham, and the agency’s interpretation exhibits grave errors.
Pitolisant is a highly cardiotoxic drug, and the QTc/cardiac safety studies which Harmony submitted to the FDA are misleading and grossly understate the risk of QT prolongation and associated cardiovascular danger. FDA review documents indicate they relied on two studies (P09-11 and P14-05), which do not appear to have been published – consistent with a long pattern of omissions and selective disclosure. The FDA’s clinical review noted that “there was a clear and direct correlation of pitolisant exposure with QTc prolongation” and that “at supratherapeutic doses, QTc increases greater than 10 msec are anticipated”

*FDA CDER Clinical Pharmacology Review, Dec 2018*

The effect of pitolisant was evaluated in clinical studies P09-11 (TQT study) and P14-05 (SAD Study) and the agency performed independent analysis of these data (Darrtis- IRT Report, Jose Vicente Ruiz et. al., 3/22/2019). The data analysis suggested that the highest therapeutic dose of 40 mg (salt form) at steady state did not cause any clinically significant QTc prolongation. However, there was a clear and direct correlation of pitolisant exposure with QTc prolongation. At supratherapeutic doses, QTc increases greater than 10 msec are anticipated. The detailed concentration QTc analysis are included in the IRT report.

*Table 6: The Point Estimates and the 90% CIs for ΔAQTcF (ms) increases at therapeutic and supra-therapeutic dose levels*

<table>
<thead>
<tr>
<th>Safety Window</th>
<th>Cmax at steady state (ng/mL)</th>
<th>ΔAQTcF (ms) &amp; 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest therapeutic Dose (i.e., 40 mg in salt form at steady state)</td>
<td>~ 73 ng/mL</td>
<td>4.2 (3.2, 5.2)</td>
</tr>
<tr>
<td>2.5-fold over highest therapeutic Dose</td>
<td>~ 175 ng/mL</td>
<td>9.8 (7.7, 11.8)</td>
</tr>
<tr>
<td>3.8-fold over highest therapeutic Dose</td>
<td>~ 280 ng/mL</td>
<td>15.5 (12, 18.9)</td>
</tr>
</tbody>
</table>

QTc prolongation of ~10 msec and ~16 msec at ~175 ng/mL and ~280 ng/ML, respectively
Although the FDA exhibited keen awareness of the risk of QTc prolongation beyond a certain dose, it was persuaded that plasma levels at the labeled 40 mg dose are safe while doses from 120 to 240 mg – tested in the two cardiac safety studies (P09-11 and P14-05) – resulted in QTc prolongation, hence indicating a safety margin. The FDA noted that 107 mg was associated with a QT prolongation of 10 msec, the typical threshold beyond which a drug is considered cardiotoxic enough to prevent approval; and that 240 mg resulted in prolongation of 12-19 msec – “Most patients who receive pitolisant are unlikely to reach exposures seen with the 106.8 mg dose, as the highest recommended dose is 35.6 mg once daily.” The agency also noted the risk of higher blood concentration of pitolisant in patients with moderate liver or kidney issues, or poor CYP3D6 metabolizers.

FDA CDER Clinical Review, Dec 2018

The Sponsor evaluated the effect of pitolisant on the QT interval in two studies (Studies P09-11 and P14-05) […] Study P09-11 was a total QT (TQT) study that evaluated doses up to 120 mg (single dose). Study P14-05 was a single ascending dose (SAD) study that evaluated doses up to 240 mg. The TQT study did not find a clinically significant QTc prolonging effect with the recommended pitolisant dose of 40 mg once daily, though a dose of 120 mg was associated with QTc prolongation of approximately 10 milliseconds (msec).

“A concentration-dependent QTc prolongation over a dose range of 40 to 240 mg was detected in this QT assessment. At steady state concentrations with the 40 mg dose, the expected mean (90% CI) increase in QTc is 4.2 (3.2 to 5.2) msec […] The highest dose tested (240 mg) provides a 1.8-fold exposure margin over the high clinical exposure scenario and the expected mean increase is 15.5 (12.0 o 18.9) msec.”

“At the recommended doses, pitolisant does not prolong the QT interval. However, patients with moderate liver impairment, moderate and severe kidney impairment, and patients taking medications that affect the metabolism of pitolisant may have higher blood concentrations of pitolisant and a higher risk of QT interval prolongation.”

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
The FDA’s interpretation of Harmony’s QT data is deeply flawed. First, although it clearly states that there is a dose-dependent QT prolongation, it incorrectly assumes that the 35.6 mg dose is below the threshold at which it manifests. The FDA simply assumes that Harmony’s assertion of average plasma levels at 35.6 mg (73 ng/mL) is correct, despite clear red flags indicating it is far higher. Second, the FDA’s entire analysis depends on the safety margins in the two cardiac safety studies (P09-11 and P14-05), which measured QT prolongation at supra-therapeutic doses of 120 to 240 mg. The problem is that these supra-therapeutic doses were only SINGLE-DOSE and would not cover the steady-state peak plasma concentrations which are 2.3 times higher what they would be after a single dose, given pitolisant’s half-life and the implied accumulation ratio.

**FDA CDER Clinical Review, Dec 2018 – indicates the QT studies were both single-dose**

““The Sponsor evaluated the effect of pitolisant on the QT interval in two studies (Studies P09-11 and P14-05) […] Study P09-11 was a total QT (TQT) study that evaluated doses up to 120 mg (single dose). Study P14-05 was a single ascending dose (SAD) study that evaluated doses up to 240 mg. The TQT study did not find a clinically significant QTc prolonging effect with the recommended pitolisant dose of 40 mg once daily, though a dose of 120 mg was associated with QTc prolongation of approximately 10 milliseconds (msec).”

**Summary of studies P09-11 (TQT study) and P14-05 (SAD study) per 2016 review paper**

The designs of the two studies and assessments of study endpoints of interest are briefly summarized below. The TQT study (40- and 120-mg single doses) was conducted during March–August 2010 whereas the high-dose SAD study (160-, 200-, and 240-mg single doses) was conducted during October–November 2014 in order to extend even higher the dose range investigated in the TQT study.

We engaged two consultants to analyze Harmony’s cardiac safety data, one a pharmacology consultant and the second a prominent expert specifically in hERG/QT and drug-induced cardiotoxicity. The pharmacology consultant characterized Harmony’s data as “intentionally misleading” and “sneaky,” stating that the “statements made about safety margins are therefore overestimated and incorrect.” The consultant strongly disputed the FDA’s interpretation of “clinically insignificant” or “clinically manageable increases in QT at supra-therapeutic doses” as they were inferred from single-dose plasma levels vs. at steady-state.

Comments by a pharmacology consultant engaged by Scorpion Capital

“Basic PK – since the half-life of Pitolisant is approximately 20 hours about half the drug levels will be circulating when the 2nd dose is administered so this is added to the new peak plasma levels on Day 2, and again on day 3, day 4 etc., until steady state plasma levels are reached (for Pitolisant about 6 consecutive days of dosing - rule of thumb for half-life – it takes approximately 6 half lives of a drug to reach steady state). This is what the “accumulation ratio” parameter exemplifies In a nutshell, the peak plasma levels of Pitolisant after 6 consecutive daily doses will be 2.3x higher than they were on Day 1 but the Day 1 plasma concentrations were used to estimate the safety margins for QTcF. Thus, the QTcT study is intentionally misleading, and the statements made about safety margins are therefore overestimated and incorrect. For example, “clinically insignificant QT increases at of only 9.8 msec at 2.5x the highest therapeutic dose” BUT THIS IS TRUE ONLY AFTER A SINGLE DOSE NOT FOR MULTIPLE DAILY DOSES. These measurements should have been made at steady state after at least 6 daily doses in order for these safety margins to be accurate – they would in fact be substantially smaller (safety margins) which may account for the reported QTcF increases seen in the sleep apnea trials.” –Pharmacology consultant engaged by Scorpion Capital
We believe the FDA made a grave error in relying upon single-dose plasma levels to infer safety margins for QT prolongation, versus using steady-state levels which are 2.3 times higher. Shockingly, the FDA CDER Clinical Pharmacology Review, in a section on pages 31 and 32 devoted to QT increases, includes a plot developed by its staff that shows QT interval increases at various plasma levels. The title of the graph states that it shows “QTc vs. steady state Cmax” – however, the data is based upon plasma levels after a SINGLE DOSE, NOT STEADY-STATE levels which are 2.3 times higher, and which means the graph is incorrect.

*FDA CDER Clinical Pharmacology Review, page 32*

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf
The same error – incorrectly using plasma levels after a single-dose but confusing them as steady-state Cmax – appears in multiple places in the FDA review document. A table immediately before the preceding graph shows a table with a column labeled “Cmax at steady state.” However, the plasma levels used to compute safety windows for the 2.5-fold and 3.8-fold dose levels are once again NOT steady state. They show plasma levels after ONE dose, and hence grossly understate the actual plasma level as well as the QT prolongation, which the FDA admits is dose-dependent.

**FDA CDER Clinical Pharmacology Review, page 31/32**

**Table 6: The Point Estimates and the 90% CIs for ΔΔQTcF (ms) increases at therapeutic and supra-therapeutic dose levels**

<table>
<thead>
<tr>
<th>Safety Window</th>
<th>Cmax at steady state (ng/mL)</th>
<th>ΔΔQTcF (ms) &amp; 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest therapeutic Dose</td>
<td>~ 73 ng/mL</td>
<td>4.2 (3.2, 5.2)</td>
</tr>
<tr>
<td>(i.e., 40 mg in salt form at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>steady state)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.5-fold</strong> over highest</td>
<td>~ 175 ng/mL</td>
<td>9.8 (7.7, 11.8)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.8-fold</strong> over highest</td>
<td>~ 280 ng/mL</td>
<td>15.5 (12, 18.9)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

175 ng/mL and 280 ng/mL plasma levels are incorrectly labeled as “steady state” when they are merely the level after a single dose.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf
We were able to locate the raw data the FDA used to construct the graph, from a later review paper that included a table from both QT safety studies P09-11 (TQT study) and P14-05 (SAD study). The table shows plasma levels after a single dose at 40mg, 120mg, 160mg, 200mg, and 240mg. Our pharmacology consultant then 1) used the single-dose plasma levels to calculate plasma levels at steady-state, and 2) used the change in QTcF vs. plasma level from another table in the same paper to develop a simple linear regression model.

Data tables for plasma levels and QT interval change after single ascending doses, from P09-11 (TQT study) and P14-05 (SAD study) per 2016 review paper

Table 2: “Pitolisant pharmacokinetic parameters in the male subjects in the two studies”

Table 3: “Estimated mean (90 % CI) placebo-corrected change from baseline (ΔΔQTcF)”
The regression analysis clearly shows that when single-dose plasma levels upon which the FDA relied are corrected to reflect steady-state levels, there is no safety margin and QT prolongation quickly spikes to dangerous levels. At 120 mg, QT prolongation is estimated at 22 msec with an upper confidence interval of 49 msec – a red alert level. Pitolisant’s PK profile indicates that a subset of patients can easily hit the plasma levels associated with 120 mg, given massive CYP2D6 liability and drug-drug interactions, as well as poor metabolizers with liver or kidney issues. The data also shows that even at the labeled dose of 35.6mg, the upper limit confidence interval is already past the danger threshold at 12 msec.

Data tables from QT studies as well our estimates which reflect corrected value:

<table>
<thead>
<tr>
<th>Dose mg</th>
<th>40 mg</th>
<th>120 mg</th>
<th>160 mg</th>
<th>200 mg</th>
<th>240 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>25</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Cmax, single dose</td>
<td>52.88</td>
<td>164.27</td>
<td>177.18</td>
<td>229.02</td>
<td>281.63</td>
</tr>
<tr>
<td>CV %</td>
<td>50.71</td>
<td>38.09</td>
<td>27.48</td>
<td>27.48</td>
<td>16.61</td>
</tr>
<tr>
<td>AUC ng*hr/mL</td>
<td>378.38</td>
<td>1399.12</td>
<td>2934.34</td>
<td>3749.36</td>
<td>5127.91</td>
</tr>
<tr>
<td>CV %</td>
<td>54%</td>
<td>45%</td>
<td>48%</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>TQT/Tmax, ms</td>
<td>3.29</td>
<td>5.27</td>
<td>11.9</td>
<td>13.3</td>
<td>9.9</td>
</tr>
<tr>
<td>Upper limit TQT, ms</td>
<td>6.23</td>
<td>8.2</td>
<td>17.1</td>
<td>18.5</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Corrected for multiple dose at steady state assuming a 51% SD:

<table>
<thead>
<tr>
<th>Dose mg</th>
<th>40 mg</th>
<th>120 mg</th>
<th>160 mg</th>
<th>200 mg</th>
<th>240 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>25</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Cmax, single dose</td>
<td>121.62</td>
<td>377.82</td>
<td>407.51</td>
<td>526.75</td>
<td>647.75</td>
</tr>
<tr>
<td>CV %</td>
<td>50.71</td>
<td>38.09</td>
<td>27.48</td>
<td>27.48</td>
<td>16.61</td>
</tr>
<tr>
<td>95% CI Upper Limit</td>
<td>245.68</td>
<td>763.20</td>
<td>823.18</td>
<td>1064.03</td>
<td>1308.45</td>
</tr>
<tr>
<td>AUC ng*hr/mL</td>
<td>870.27</td>
<td>3217.98</td>
<td>6748.98</td>
<td>8623.53</td>
<td>11794.19</td>
</tr>
<tr>
<td>CV %</td>
<td>54%</td>
<td>45%</td>
<td>48%</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>TQT/Tmax, ms*</td>
<td>4.67</td>
<td>22.19</td>
<td>24.23</td>
<td>32.38</td>
<td>40.66</td>
</tr>
<tr>
<td>Upper limit TQT, ms*</td>
<td>13.16</td>
<td>48.55</td>
<td>52.66</td>
<td>69.13</td>
<td>85.85</td>
</tr>
</tbody>
</table>

Source: Pharmacology analysis commissioned by Scorpion Capital

Single does plasma levels upon which the FDA relied massively underestimate the risk of QT prolongation.

Corrected plasma levels show QT prolongation quickly spikes to dangerous levels, with no safety margin, and becomes dangerous even at the upper limit CI at the dose on the label.
We detail below the methodology used by our pharmacology consultant to correct the plasma levels used by the FDA in assessing cardiotoxicity, as well the simple regression model based on data tables from Harmony’s two QT studies. We note the consultant’s blunt conclusion: “there is no safety margin using the actual data and anticipated steady state level….”

**Methodology and regression model used to correct single-dose QT data to steady-state plasma levels**

“I graphed all of the single dose plasma levels vs change in TQT and created a linear regression line. The resulting equation is Y=14.62 x “X”+53.34. Solving for X (the TQT change) one can then determine the correct TQT for a certain plasma level (“Y”). The plasma levels at steady state were determined from the single dose plasma levels by multiplying by 2.3. Solving for “Y” at both the mean and the upper limit of the 95% CI (2SD). I used 51% for the plasma variability as I do not believe the other values but could easily assess using them. By this method, the actual TQT at steady state is 4.7, 22, 24, 32 and 41 ms (mean) at doses of 40, 120, 160, 200 and 240 mg. At the upper CI the TQT at steady state is 14, 49, 53, 69 and 86 ms at doses of 40, 120, 160, 200 and 240 mg, respectively at steady state. **So, no, there is no safety margin using the actual data and anticipated steady state level (2.3 accumulation ratio).**” – Pharmacology consultant engaged by Scorpion Capital

**Plot of Single Dose PK vs TQT change from Baseline**

![Plot of Single Dose PK vs TQT change from Baseline](https://pubmed.ncbi.nlm.nih.gov/26879827/)

Source: https://pubmed.ncbi.nlm.nih.gov/26879827/
CYP2D6 liability and drug-drug interactions amplify toxicity; the FDA’s assessment was based on misleading data.
Pitolisant is plagued by a potent CYP2D6 liability and extensive drug-drug interactions, which can exponentially multiply the risk of QT-related cardiotoxicity as well as adverse effects related to liver, kidney, or other toxicity. Pitolisant – as noted on the label – “is primarily metabolized by CYP2D6” which is an enzyme that is mainly expressed in the liver and is responsible for the metabolism and elimination of certain drugs. A certain percentage of the population are known as “poor CYP2D6 metabolizers,” which means they have a CYP2D6 genetic phenotype that prevents them from properly metabolizing pitolisant. As a result, blood concentrations of the drug can spike far beyond levels that are safe. The FDA noted this concern on the label, and recommended half the normal dose for poor CYP2D6 metabolizers, stating that “3 to 10% of Caucasians and 2 to 7% of African Americans are poor metabolizers.”

*Pitolisant package insert and full prescribing information, excerpts – mentions CYP2D6 dose adjustments for poor metabolizers*

- Poor Metabolizers of CYP2D6: Maximum recommended dosage is 17.8 mg once daily (2.5)

8.8 CYP2D6 Poor Metabolizers

Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher pitolisant concentrations than normal CYP2D6 metabolizers [see Dosage and Administration (2.5), Clinical Pharmacology (12.3, 12.5)].

CYP2D6 safety issues are not only triggered by genetically poor metabolizers, but also by those simultaneously taking other drugs than inhibit CYP2D6. The label therefore has a separate section for CYP2D6 inhibition due to drug-drug interactions, and once again recommends half the regular dose in this case. As we shall show, danger due to pitolisant’s drug-drug interactions is inevitable and unavoidable, as it interacts strongly with medications like SSRI’s and other antidepressants that are widely prescribed for narcolepsy and cataplexy.

*Pitolisant package insert and full prescribing information, excerpts – CYP2D6 dose adjustments due to potential drug-drug interactions*

---

**DRUG INTERACTIONS**

- Strong CYP2D6 Inhibitors: Maximum recommended dosage is 17.8 mg once daily (2.4, 7.1)

### 7.1 Drugs Having Clinically Important Interactions with WAKIX

**Table 2: Clinically Significant Drug Interactions with WAKIX**

<table>
<thead>
<tr>
<th>Effect of Other Drugs on WAKIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 Inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Implication:</th>
<th>Concomitant administration of WAKIX with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention or Management:</td>
<td>Reduce the dose of WAKIX by half [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].</td>
</tr>
</tbody>
</table>

The FDA’s assessment of CYP2D6 safety issues and resulting dosage adjustments are based on highly misleading data from Harmony, which we believe flagrantly misrepresents the potential for elevated plasma levels of pitolisant and associated cardiovascular and other toxicity. We note comments from a pharmacology consultant who we engaged to review the materials upon which the FDA relied, who expressed concern that the risk of high blood concentration and potential complications “are downplayed across the board”: “plasma levels of drugs relying on 2D6 for clearance/metabolism vary widely,” with studies showing that some 2D6-cleared drugs “possess 30 to 40-fold variability in their plasma concentrations”; and that drug-drug interactions are a significant risk as it is common for narcolepsy patients to “have co-morbidities and/or to be treated with” drugs like antidepressants that inhibit CYP2D6.

Assessment by pharmacology consultant that drug-drug interactions and CYP2D6 are downplayed

“Pitolisant is mostly metabolized by CYP450 2D6 and the metabolic phenotype of this enzyme varies widely across individuals (ultra-low, normal, high and ultra-high metabolizers). As mentioned before, the plasma levels of drugs relying on 2D6 for clearance/metabolism vary widely in patients depending upon their 2D6 metabolic phenotype. Many psychotropic drugs need to be metabolized prior to excretion in the urine. In the 1960s it was shown that tricyclic antidepressants possess 30 to 40-fold variability in their plasma concentrations due to the polymorphic expression of CYP2D6 (Hammer & Sjöqvist 1967; Bertilsson et al., 1980). Since it is common for both narcolepsy and sleep apnea patients to have co-morbidities and/or to be treated with antidepressants including tricyclic antidepressants, these potential drug-drug interactions between pitolisant and antidepressants are of note and important to consider. However, the potential for changes in pitolisant levels and associated cardiovascular complications are downplayed across the board.” – Pharmacology consultant engaged by Scorpion Capital

Source: Pharmacology analysis commissioned by Scorpion Capital
The CYP2D6 concerns voiced by our pharmacology consultant are consistent with the scientific literature on problems with H3 receptor antagonists/inverse agonists, particularly ones with the same non-imidazole structure as pitolisant, as we discussed in a previous section. We further noted papers by pharma companies like Abbott and Evotec which synthesized pitolisant and concluded that it is plagued by severe problems including cardiotoxicity and CYP2D6 issues, and who also indicated that Bioprojet’s claims were not reproducible in their labs. We again excerpt some of those papers here: pitolisant is a “potent inhibitor of CYP2D6 and hERG”; “our laboratory findings suggest that CYP2D6 inhibition…would likely be important hurdles for this novel compound”; and that “in vitro profiling in our laboratory (and others) suggests that BF2.639 [pitolisant] has both a CYP2D6 liability…and potent hERG channel K+ blockade.”

2010 review paper, Raddatz et al
shorter brain residence time [44]. The development and druggability of tiprolisant (BF2.649 5), reportedly in Phase II clinical trials for a number of potential indications, including cognitive enhancement, have been questioned, since it had limited oral bioavailability, was a potent inhibitor of CYP2D6 and hERG, and also had the potential for inducing phospholipidosis, possibly due to the high clogP (4.8) [76].

2009 paper by Evotec scientists
Bioprojet’s H3R antagonist BF2.649 (Table 2) exhibits potent binding to native human (IC₅₀ = 5.3 nM), rat (Kᵢ = 17 nM) and mouse (Kᵢ = 14 nM) cortical H3 receptors. Further in vitro profiling in our laboratory (and others [15]) suggests that BF2.649 has both a CYP 2D6 liability (IC₅₀ = 0.4 μM) and potent hERG K⁺ channel blockade (IC₅₀ = 0.49 μM). BF2.649 is also reported to have poor PK profiles in both rat and dog (5% and 2% bioavailability).

2008 paper by Abbott scientists
these species. BF2.649 is presently under clinical investigation in several Phase II trials for the treatment of schizophrenia, ADHD, dementia and Parkinson’s disease. (www.stanleyresearch.org/programs/trialgrants.htm). From the development point of view, our laboratory findings suggest that CYP2D6 inhibition, potent hERG binding and the potential for phospholipidosis would likely be important hurdles for this novel compound.

We have already noted – in the section on cardiotoxicity – that pitolisant’s steady-state plasma levels are far higher and more variable/unpredictable than asserted by Bioprojet and Harmony. Pitolisant displays a dose-dependent risk of QT prolongation and cardiovascular danger, which we believe Harmony is trying to conceal by significantly understating actual blood levels of the drug. The fact that pitolisant has a CYP2D6 liability further escalates an already significant risk, as already elevated plasma levels can spike many multiples from there. The critical question then becomes: how much do pitolisant levels increase in poor 2D6 metabolizers? The FDA relied upon an absurdly small Harmony PK study in CYP2D6 poor metabolizers (n=3) to conclude that steady-state plasma levels in such patients are twice those of normal metabolizers – 73 ng/ML in normal metabolizers at the 35.6mg dose, and 153 ng/mL in poor metabolizers – and hence recommends cutting the dose in half.

Pitolisant package insert and full prescribing information, excerpts

12.5 Pharmacogenomics

Approximately 3 to 10% of Caucasians and 2 to 7% of African Americans generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. The AUC of pitolisant was approximately 2.4 times higher in CYP2D6 poor metabolizers than in normal metabolizers and is similar to the exposure of pitolisant when WAKIX is administered concomitantly with a CYP2D6 inhibitor [see Dosage and Administration (2.5). Drug Interactions (7.1)].

In CYP2D6 poor metabolizers, the Cmax of pitolisant is 153 (151 to 157) ng/mL and the AUC is 1920 (1854 to 2000) ng*hr/mL after steady state dosing with 35.6 mg once daily.

FDA CDER Clinical Pharmacology Review

CYP2D6 Genetic Deficiencies:
An approximate 2-fold increase in exposure was observed in CYP2D6 poor metabolizers (PMs) as compared to CYP2D6 normal metabolizers (NMs). Additionally, a dedicated drug interaction study with paroxetine (a strong CYP2D6 inhibitor) also resulted in a similar increase in exposure of pitolisant which supports the conclusion that exposures can be expected to be 2x -fold higher in CYP2D6 PMs. Therefore, the dose of WAKIX should be capped at 17.8 mg/day in known CYP2D6 PMs. The details are provided in Clinical Pharmacology Questions (3.3).

However, simply halving the dose does little to alleviate the danger. First, most patients do not know their CYP2D6 phenotype, and our interviews with 20 pitolisant prescribers indicate that no doctors are bothering to genetically test their patients. It is simply inevitable that poor metabolizers are being prescribed the max 35.6 dose – and hence the predictable spike in serious adverse events per the FDA FAERS database. Second, Harmony’s sales reps aggressively push it as an ultra-safe drug, creating even more complacency and danger. The FDA’s approach to mitigating CYP2D6-related risks – merely suggesting a smaller dose – is therefore naïve and defies clinical and commercial realities. Third, the CYP2D6 PK study upon which the FDA relied exhibits numerous red flags, consistent with what we believe to be Bioprojet’s long pattern of scientific and clinical fraud. The study results don’t appear to be published, and the full data appears to be buried and missing from even the EMA and FDA review packages. A Clinical Trials entry contains only a few shreds of basic info:

**Bioprojet Phase 1 PK study in CYP2D6 metabolizers – ClinicalTrials.gov entry**

*Study to Assess the Absorption, Distribution, Metabolism and Excretion (ADME) of [14C]-Pitolisant in Healthy Male Volunteers*

<table>
<thead>
<tr>
<th>Study Design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Type</strong>:</td>
<td>Interventional (Clinical Trial)</td>
</tr>
<tr>
<td><strong>Actual Enrollment</strong>:</td>
<td>8 participants</td>
</tr>
<tr>
<td><strong>Allocation</strong>:</td>
<td>Non-Randomized</td>
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<tr>
<td><strong>Intervention Model</strong>:</td>
<td>Parallel Assignment</td>
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<tr>
<td><strong>Masking</strong>:</td>
<td>None (Open Label)</td>
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<tr>
<td><strong>Primary Purpose</strong>:</td>
<td>Basic Science</td>
</tr>
<tr>
<td><strong>Official Title</strong>:</td>
<td>An Open Label, Single-Period Repeated Dose Study Designed to Assess the Mass Balance Recovery, Metabolite Profile and Metabolite Identification of [14C]-Pitolisant, at Steady-State Conditions, in Healthy CYP2D6 Genotyped Male Subjects</td>
</tr>
<tr>
<td><strong>Study Start Date</strong>:</td>
<td>July 2016</td>
</tr>
<tr>
<td><strong>Actual Primary Completion Date</strong>:</td>
<td>August 2016</td>
</tr>
<tr>
<td><strong>Actual Study Completion Date</strong>:</td>
<td>August 2016</td>
</tr>
</tbody>
</table>

Source: https://clinicaltrials.gov/ct2/show/NCT02929342
The FDA CDER Clinical Pharmacology Review contains a bit more information about the CYP2D6 PK study, but it appears they were only provided with a summary and not the underlying data. The red flags are obvious. First, it had only 8 patients, and only 3 were poor CYP2D6 metabolizers – in other words, the FDA’s estimate of steady-state plasma levels and dosage adjustment are based on pharmacokinetics in merely *three* poor metabolizers. The metabolic genotype/phenotype of CYP2D6 varies widely from individual to individual, leading to massive variability in plasma levels. Limiting a study to n=3 such participants suggests an attempt to cherry-pick and present misleading data that understates the variability. CYP2D6 has dozens of phenotypes, and depending on the phenotype an individual’s level of CYP2D6 function may be none, little, decreased/intermediate, normal, or rapid. For example, Wikipedia lists a table of dozens of CYP2D6 phenotypes and their level of activity.

CYP2D6 phenotypes and their level of metabolic activity

<table>
<thead>
<tr>
<th>CYP2D6 enzyme activity for selected alleles[8][17]</th>
<th>CYP2D6*17</th>
<th>decreased</th>
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<tbody>
<tr>
<td>Allele</td>
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<td>CYP2D6*1</td>
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<td></td>
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<tr>
<td>CYP2D6*14</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*15</td>
<td>none</td>
<td></td>
</tr>
</tbody>
</table>

Source: https://en.wikipedia.org/wiki/CYP2D6
The second red flag: Bioprojet/Harmony don’t state which CYP2D6 phenotypes were selected for the three “poor” metabolizers tested – how are “poor” and “normal” defined? Further muddying the waters, the terms NM (“normal metabolizers”) and EM (“extensive metabolizers”) are used interchangeably for the 5 “normal” subjects, although the terms refer to different CYP2D6 phenotypes. The FDA’s description, which we suspect is a cut and paste summary from the company, is tellingly vague: “CYP2D6 alleles tested and genotyping methods were appropriate for determining CYP2D6 PM [poor metabolizer] and NM [normal metabolizer] status.” In the absence of this information – given the already absurd n=3 – the steady plasma estimate of poor metabolizers is meaningless. We suspect Bioprojet simply chose metabolizers with CYP2D6 phenotypes for decreased activity vs. those with little to none, thereby dramatically underestimating plasma levels.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf
The third red flag: the ranges for the asserted plasma level in poor metabolizers are inconsistent. One section in the label says that “in CYP2D6 poor metabolizers, the Cmax of pitolisant is 153 (151 to 157) ng/mL” – a range so tight that it strains credibility, leading us to wonder if Bioprojet simply chose the plasma levels they wanted and phenotyped those patients in hindsight. And then, while one part of the label asserts this impossibly tight range of 151 to 157 ng/mL, a chart above it is more telling with a FOUR-FOLD higher plasma level, a dangerous level of variability across just three patients. Moreover, the chart is misleading, as it uses a log scale which makes the plasma level variability in poor metabolizers look less dramatic. We note that studies have shown 30-40 fold variability in plasma levels in CYP2D6-metabolized drugs.

*Pitolisant full prescribing information from the label, section 12.3, p13*

**CYP2D6 Poor Metabolizers**

The pharmacokinetics of pitolisant were evaluated in 3 subjects who were CYP2D6 poor metabolizers (PMs) and 5 subjects who were CYP2D6 extensive metabolizers (EMs). All subjects received WAKIX 17.8 mg daily for 7 days. Exposure of pitolisant in CYP2D6 PMs is summarized in Figure 3.

Figure 3:  Pitolisant Pharmacokinetics in CYP2D6 Poor Metabolizers

Up to four-fold change in plasma levels at 90% confidence interval in poor CYP2D6 metabolizers despite only testing 3 patients

Dots = Geometric least square mean ratios. Error bars = 90% CI; reference dashed lines are 0.8 and 1.25.

AUC$_{0-24}$ = area under the curve from time 0 to 24 hours post-dose; C$_{max}$ = maximum plasma concentration.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000ClinPharmR.pdf
And a fourth red flag, one we find potentially nefarious: it’s unclear what dose was used to determine the plasma level in poor vs. normal CYP2D6 metabolizers. We speculate whether Harmony may have misled the FDA, given the rampant statistical tricks across its papers and trials – using a 40mg dose to determine the plasma level in normal metabolizers, but only a 17.8mg dose in the three patients who were poor metabolizers. This would make the plasma level increase in poor metabolizers appear less worse than it is. Note below that the FDA CDER Clinical Pharmacology Review states that it was 40 mg, while the prescribing instruction in the label – which contains the graph – states that it was 17.8 mg. Notably, the ClinicTrials.gov entry doesn’t mention dose at all.

**FDA review docs versus full prescribing information from the label**

**CYP2D6 Genetic Deficiencies:**
The PK of pitolisant in PMs of CYP2D6 vs. Normal metabolizers (NM) of CYP2D6 was assessed in 8 genotyped healthy adult, male subjects in a mass balance clinical study (P15-02). The PK after single dose as well as after steady state (on day 7) at 40 mg dose (in salt form) was used to compare the exposure in PMs (N=3) vs. NM (N=5). CYP2D6 alleles tested are:

**CYP2D6 Poor Metabolizers**
The pharmacokinetics of pitolisant were evaluated in 3 subjects who were CYP2D6 poor metabolizers (PMs) and 5 subjects who were CYP2D6 extensive metabolizers (EMs). All subjects received WAKIX 17.8 mg daily for 7 days. Exposure of pitolisant in CYP2D6 PMs is summarized in Figure 3.

**Figure 3: Pitolisant Pharmacokinetics in CYP2D6 Poor Metabolizers**

The danger from elevated pitolisant plasma levels in poor CYP2D6 metabolizers is self-evident. Even using Harmony’s asserted plasma level of 153 ng/mL – a misleadingly low number – it can spike by four-fold within a 90% CI per their own graph in the label. That results in 612 ng/mL, and far higher at a 95% CI. The expected QT prolongation at 612 ng/mL is 38 msec - well into the danger zone for cardiovascular toxicity - using the regression model developed by our pharmacology consultant using Bioprojet’s papers (see section on cardiac safety data). If, as we suspect, the CYP2D6 study used a 17.8mg dose (half the normal dose) to calculate the 153 ng/mL plasma level, then the true level is 306 ng/mL. At a four-fold change, the 306 can spike to 1224 ng/mL which leads to an expected QT prolongation of 80 msec, which of course explains the prevalence of serious cardiac events in the FDA’s adverse events database as well as potentially the cardiac-related fatality in the HAROSA sleep apnea trial. Merely suggesting half the dose per the label does little to nothing to mitigate the risk.

Regression analysis shows expected QT prolongation at various plasma levels

<table>
<thead>
<tr>
<th>Dose mg</th>
<th>40 mg</th>
<th>120 mg</th>
<th>160 mg</th>
<th>200 mg</th>
<th>240 mg</th>
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<td>25</td>
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<td>377.82</td>
<td>407.51</td>
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</tr>
<tr>
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<td>38.09</td>
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<td>16.61</td>
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<tr>
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<td>763.20</td>
<td>823.18</td>
<td>1064.03</td>
<td>1308.45</td>
</tr>
<tr>
<td>AUC ng*hr/mL</td>
<td>870.27</td>
<td>3217.98</td>
<td>6748.98</td>
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<td>54%</td>
<td>45%</td>
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<td>TQT/Tmax, ms*</td>
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<td>22.19</td>
<td>24.23</td>
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<td>48.55</td>
<td>52.66</td>
<td>69.13</td>
<td>85.85</td>
</tr>
</tbody>
</table>

Regression formula (see slide __) indicates 38-80 msec QT prolongation at plasma levels within the range for poor CYP2D6 metabolizers of pitolisant
CYP2D6 safety issues are triggered not only by genetics but by **drug-drug interactions that inhibit CYP2D6 activity**. Both the FDA and EMA reviews list a broad range of potential interactions that can cause plasma levels to spike, SSRI’s in particular which the reviews state “are potent inhibitors of CYP2D6” and that “co-administration of pitolisant with inhibitors of CYP2D6 should be done with caution.” Our interviews with 20 prescribers indicate that virtually every patient is on multiple medications, especially SSRI’s which are extensively prescribed for narcolepsy as well as cataplexy – suggesting that a **large percentage of pitolisant patients can be expected to have plasma levels at least double** what’s stated as the average on the label.

**EMA pitolisant assessment report**

SSRIs are potent inhibitors of CYP2D6, pitolisant is a substrate and a weak inhibitor of CYP2D6. The inhibition of CYP2D6 by paroxetine could lead to 2-fold increase of pitolisant exposure. Given the safety profile of pitolisant from phase II and III trials, it can be concluded that co-administration of pitolisant with inhibitors of CYP2D6 should be done with caution.

**FDA pitolisant review documents**

**Drug Interactions:** Clinically important interactions with pitolisant can be expected with concomitant use of strong CYP2D6 inhibitors and inducers, Histamine 1 (H1) antagonists, drugs that prolong the QT interval, and sensitive CYP3A4 substrates.

4.5 Interaction with other medicinal products and other forms of interaction

**Reviewer’s Comment:** This section of the labeling discusses several important potential drug-drug interactions between pitolisant and the following types of medications: tricyclic and tetracyclic antidepressants, antihistamines, QT interval-prolonging substances, CYP3A inducers, CYP2D6 inhibitors, substrates of CYP3A4 and CYP2D6, hormonal contraceptives, and substrates of OCT1.

We further note an inevitable combination which further escalates the danger: patients that are already poor CYP2D6 metabolizers who are concurrently taking a CYP2D6 inhibiting drug like an SSRI or common OTC antihistamines. Patients don’t know their CYP2D6 phenotype and the probability of their being on such drugs is high. This suggests a doubling then another doubling of plasma levels using the 2X increase Harmony asserts, which we think is underestimated. At a potential 4X increase, patients would be hit 153 ng/mL times 4 (fold change at 90% CI per the label for poor metabolizers) times 2 (Harmony’s claimed fold change in the presence of CYP2D6-inhibiting drugs), which equals 1224 ng/mL – a red-alert level for cardiotoxicity.


Common antihistamines and antidepressants are CYP2D6 inhibitors e.g, Benadryl, Claritin, Prozac

- Amiodarone (Cordarone)
- Bupropion (Wellbutrin)
- Chlorpheniramine (Chlor-Trimeton)
- Chloroquine (Aralen)
- Chlorpromazine (Thorazine)
- Cinacalcet (Sensipar)
- Diphenhydramine (Benadryl)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Halofantrine (Halfan)
- Haloperidol (Haldol)

- Imatinib (Gleevec)
- Paroxetine (Paxil)
- Perphenazine (Trilafon)
- Propafenone (Rythmol)
- Propoxyphene (Darvon)
- Quinacrine (Atabrine)
- Quinidine (Quinidex, etc)
- Quinine
- Terbinafine (Lamisil)

Paper indicates all five common antihistamines are strong CYP2D6 inhibitors

Inhibitory effects of H1-antihistamines on CYP2D6- and CYP2C9-mediated drug metabolic reactions in human liver microsomes

“Conclusion: All five H1-antihistamines studied inhibited CYP2D6 markedly…”
The FDA’s suggestion on the label to halve the dose to 17.8mg when pitolisant is taken with “strong CYP2D6 inhibitors” does little to mitigate the danger – we again emphasize that this assumes that patients know their CYP2D6 phenotype, which they generally do not. Our search of every major pitolisant/narcolepsy patient support group on Facebook, with thousands of members and posts, didn’t result in a single post where a patient mentioned being tested for their CYP2D6 phenotype. However, posts frequently indicate that patients are on pitolisant PLUS multiple SSRI’s or antidepressants PLUS other CYP2D6 inhibitors like OTC antihistamines – a recipe for potential tragedy. Moreover, numerous posts indicate that doctors as well as Harmony’s specialty pharmacy are telling patients the opposite: that a CYP2D6 inhibitor like an antihistamine DECREASES pitolisant levels, when in fact the opposite is true. Some representative examples:

**Patient who is a nurse is taking pitolisant plus Benadryl and incorrectly thinks they cancel each other out vs. increasing pitolisant plasma levels**

Narcolepsy Support Group

***

So...... right before going to sleep last night a thought ran through my head as I was taking my night time medications. One of those medications is OTC sleep aid diphenhydramine, I’m a Nurse, so I thought to myself, Benadryl is an antihistamine. My daytime Narcolepsy medication is Wakix..... which increases histamine in your brain. So this whole time I’ve been on Wakix, I didn’t put two and two together lol.... Wakix and Benadryl are counter active!!!! Does anyone have any other kind of sleep aid that works for them at night?

**Pitolisant patient indicates another doctor prescribed an antihistamine as well**

Wakix (Pitolisant) for Narcolepsy/IH  -Updated group

Jan 11, 2022

Is anyone prescribed anything to be able to stay asleep? My doctor (different from the one who prescribed the Wakix) just prescribed me Hydroxyzine which is an antihistamine, not sure if that super makes sense?
Facebook posts by pitolisant patients indicate that not only are pharmacies and doctors telling them that it’s fine to combine it with antihistamines, but that doctors are taking it one step further and indicating that antihistamines reduce the effects of pitolisant – when in fact they cause its blood concentration to spike.

**Pitolisant patient who is on multiple antihistamines plus allergy injections says doctor “doesn’t think there will be a problem.”**

My Wakix prescription was finally approved and it should arrive on Monday!! 🎉
I’m slightly concerned about how my allergy shots and antihistamine use will affect it though. I’ve been getting allergy shots for a few years and I’m at the maintenance dose, so I only go once monthly. However, I HAVE TO take an antihistamine before getting each shot. From what I’ve read, I’m expecting that Wakix just won’t be super effective on those days. Aside from those days, I want to stop taking Zyrtec, so I’ve been slowly reducing and spacing out doses.

Does anyone have experience taking Wakix while getting allergy shots and/or taking antihistamines semi regularly?

Edited to add: my sleep doctor doesn’t think there will be a problem, but I’m wary of that...so I would appreciate hearing from some of your experiences!

**Pitolisant patient says her doctor “recommended taking an antihistamine...to ‘turn off’ the effects of Wakix”**

I started wakix about two weeks ago and hated it at first because of the insomnia. Today....I got so much done it was incredible. For the insomnia, my dr recommended taking an antihistamine (Zyrtec, Benadryl, etc) to “turn off” the effects of Wakix and it has definitely helped!! Definitely ask your dr first though!! I’m not trying to give anyone medical advice!! But I am sooo thankful for Wakix 😊😊😊😊

I don’t think I’ve ever been this awake before!!!!

**Pharmacy and doctor both told patient that an antihistamine “was ok”**

Edit **What were you told by your Dr or the pharmacy about Wakix and antihistamines? I know benadryl is a no go, but I thought Zyrtec was okay. That’s what I was told by the pharmacy. I told my Dr I stopped wakix because it wasn’t working well and I couldn’t sleep at night. I mentioned taking Zyrtec and he said that’s why it didn’t work, because of the zyrtec. When before he told me it was okay.**

Source: Facebook patient support groups
>Thirteen deaths during the pitolisant development program; case narratives are consistent with known toxicity
A key early warning sign was the occurrence of 13 deaths during the pitolisant development program, as noted by the FDA in its safety review. The FDA noted 9 deaths as of the NDA data cutoff date in Feb 2019, and 4 thereafter as of March 2020: “nine deaths occurred in the pitolisant development program; all occurred in patients receiving pitolisant” – that is, 100% of fatalities were in the treatment arm and none for patients on placebo. The FDA’s assessment gives Harmony the benefit of the doubt, given the flawed nature of the accelerated approval process. However, the review clearly telegraphs the agency’s skittishness and a “wait and see” posture pending safety signals from the post-marketing period. As we shall show, the prevalence of serious adverse events now confirms the FDA’s concerns, particular around QT prolongation and cardiotoxicity where the agency conveyed its acute interest: “The postmarketing data should also be monitored for sudden deaths and cardiovascular and respiratory adverse reactions.”

9 deaths through NDA data cutoff date in 2019 – all deaths were on pitolisant and none on placebo, per FDA CDER Clinical Review (Solages, Sep 28, 2020)

The Sponsor submitted narrative summaries for all deaths that occurred in the clinical development program in the NDA and submitted an update (with one additional death) in the 120-day safety report. Nine deaths occurred in the pitolisant development program; all occurred in patients receiving pitolisant (Table 35). Of the nine deaths, six occurred in male patients. One death occurred in the open-label, long-term safety narcolepsy study (HARMONY

4 additional deaths through March 2020, per same review

The Applicant has provided case narratives for four additional deaths that have occurred since the 120-day safety update. One death was reported in the U.S. EAP, one death was reported in Study P15-11 (the European Post-Authorization Safety Study), and two deaths were reported in the Study P15-13 (the ongoing phase 3 efficacy and safety study in patients with OSA).
Nine of the deaths are noted in a table on p10 of the CDER review. Six were sudden deaths (four found dead at home) that could have been due to heart failure – no autopsies were performed. Of these six, two were officially classified as cardiac events. The list includes: 1) 64-year old female who “went into cardiac and respiratory arrest 4 days after starting pitolisant”; 2) 58-year old male “found dead at home 2.5 months after the initiation of treatment” due to “acute cardiac and pulmonary insufficiency”; 3) 73-year old female “found dead at home” where oddly the “investigator thought patient death could be related to hot weather”; 4) 53-year old died at home after reporting dyspnea; 5) 39-year old “found dead at home 2 months after randomization” with “several empty boxes of medication”; 6) 71-year old male who died 31 days after discontinuing pitolisant, due to acute respiratory distress, after already being hospitalized, without the report stating when the hospitalization occurred with respect to pitolisant treatment.

Table 4: Deaths in the Pitolisant Development Program (All Indications) by 120-Day Safety Update, FDA CDER Clinical Review (Solages, Sep 28, 2020), p10-11

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
Of the 4 additional deaths, 2 were sudden deaths that could also have been heart failure, with all 4 patients on the highest dose of pitolisant (35.6mg): 1) a 43-year old female on no other medications but pitolisant, where the case narrative surprisingly provides no information on cause of death but where the investigator nonetheless “assessed the event as not related to pitolisant”; 2) a 63-year old female where an ECG abnormality during the trial was “assessed as not clinically significant.” The FDA reviewer disagreed and stated that “an association with pitolisant cannot be ruled out.” Of the 2 other deaths, one was a 62-year old who died of pulmonary edema and a 38-year old who committed suicide. Although the reviewer indicated “no clear association” with pitolisant, we note an alarming number of similar adverse events since approval, per the FAERS database, whether pulmonary edema or psychiatric ones such as suicidal fixation.

**FDA comments on 4 additional deaths after 120-day safety update, FDA CDER Clinical Review (Solages, Sep 28, 2020), p11-12; case narrative of sudden death of a 43-year old on pitolisant**

*Two additional deaths occurred in patients in the OSA development program; a total of 5 deaths have occurred in the OSA program. Although these patients had co-morbid health conditions that could have contributed to their risk of death and although patients with OSA have a higher risk of sudden death, an association with pitolisant cannot be ruled out based on the available data.*

- Sudden death was reported in a 43-year-old female with a medical history of obstructive sleep apnea and obesity. No concomitant medications were reported. The patient completed the double-blind treatment period and entered the open-label extension on [information redacted]. Pitolisant was titrated to a dose of 35.6 mg. The patient died suddenly at home on [information redacted]. The patient had not reported any adverse events during the study. The patient reportedly had a visit with her primary care physician one month prior to her death during which complained of back pain. She was advised to lose weight and quit smoking at that time. The Investigator assessed the event as not related to pitolisant.

Source: [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf)
The FDA also discussed two non-fatal cardiac events: 1) a cardiac arrest in a 49-year-old female, based on a European post-marketing Serious Individual Case Safety Report, where duration of pitolisant exposure wasn’t available but which was “notable given reports of sudden death” in the pitolisant sleep apnea trials; and 2) a 60-year old female with dizziness one month after starting pitolisant, transient ischemic attack, and QT prolongation, where the FDA reviewed stated a correlation with pitolisant “cannot be definitively established or ruled out.”

*FDA comments on cardiac arrest in 49-year old, FDA CDER Clinical Review (Solages, Sep 28, 2020)*

A reported ICSR of cardiac arrest in a young (49-year-old) female patient is notable given the reports of sudden death in the OSA development program. The patient has a medical history that was remarkable for narcolepsy, obesity, diabetes, and hypertension. The duration of exposure to pitolisant is not included in the case report. The patient was also prescribed methylphenidate. Both pitolisant and methylphenidate were discontinued. The patient recovered.

*...and on 60-year old with dizziness, ischemic attack, and QT prolongation*

A 60-year-old female with medical history of narcolepsy, two prior transient ischemic attacks, atherosclerosis, bilateral carotid dysplasia, hypertension, hypercholesterolemia, depression, fibromuscular dysplasia, asthma, thyroid dysfunction, angioedema, cephalalgia, and first-degree atrioventricular block at screening. She experienced sudden onset of dizziness with nausea approximately one month after the first dose of pitolisant. Accompanying symptoms included erratic gate with deviation to the right side, paresthesia of the right hemi-face, malaise, and brief loss of consciousness. Findings on clinical examination included a right carotid murmur and known muscular strength weakness on the right side; clinical examination was otherwise unremarkable. She was given a diagnosis of transient ischemic attack and discharged home on the day of presentation. She was reported to be symptom-free at the time of discharge. She continued to receive pitolisant 40 mg once daily and completed the study. Other adverse events reported during the study by this patient included prolonged QTc, nonspecific polarization abnormality, pericarditis, increased serum GGT, headache, depression, bronchitis, otitis, increased weight, and cataplexy.

*Reviewer comment: This patient had a prior history of TIA and significant risk factors for TIA and stroke. The TIA resolved, and the patient was able to complete the study. No clear temporal relationship between pitolisant treatment and the onset of the adverse event is evident, although a correlation between TIA and pitolisant cannot be definitively established or ruled out based on this single case.*

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
Throughout the FDA’s discussion of the fatalities, the deference afforded Harmony via the rare drug/accelerated approval pathway is evident. Despite the number of suspicious deaths, it concluded that “no clear signal for serious dysrhythmias or QT prolongation emerged in the clinical development program.” However, few patients had been exposed to pitolisant at the time and the FDA clearly relied upon the small number of serious adverse event reports. With those numbers now spiking and individual case narratives clearly indicating a safety signal, we think the FDA will be less forgiving. We note numerous statements by the FDA reviewer that are now flatly contradicted by post-approval reports.

*FDA review clearly indicates its reliance on the lack of reported serious adverse events at the time of approval in 2019 – now contradicted by the facts (FDA CDER Clinical Review (Solages, Sep 28, 2020)) (e.g., electrocardiogram abnormalities, increased risk of cardiovascular or respiratory events). Of note, cardiac, vascular, and pulmonary adverse events have not been reported frequently in the postmarketing period (see Postmarketing Data), either in the United States or in Europe (where pitolisant has been available for more than 4 years). A thorough QT (TQT) study submitted to the

association with pitolisant exposure has not been established. Cardiovascular and pulmonary adverse reactions were infrequently reported in the postmarketing period, both in the United States and in Europe (where pitolisant has been available since 2016). In patients with

**Reviewer comment:** Based on the clinical information presented, the reported TEAE of prolonged QT may have been spurious. No clear signal for serious dysrhythmias or QT prolongation emerged in the clinical development program. Patients in the dementia and Parkinson’s disease trials reported cardiovascular adverse events including cardiac failure, myocardial infarction, hypertension, and angina. Most of these patients had underlying risk factors for cardiovascular disease and most of these events occurred in the open-label phase of the clinical trials. Therefore, whether there is a correlation between pitolisant and these other cardiovascular events is unclear.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
>FDA’s sensitivity to potential CNS and hepatic safety signal will now be highly problematic for Harmony
QT prolongation and cardiac events are not the only ones where the FDA’s reviews indicate the agency’s skittishness and a wait-and-see posture pending safety signals from the post-marketing period. The FDA also noted a seizure in a European post-marketing Serious Individual Case Safety Report, stating that while none were observed in clinical trials, that the case report “is notable” and that “seizures and cardiovascular events are of special interest.” The FDA conveys its keen interest in “seizures and convulsions” several times – which we think is problematic for Harmony for two reasons. First, the FDA’s database now contains a number of serious adverse event reports related to seizures, indicating a safety signal; and two, seizures are often one of the first symptoms of QT prolongation. We note a paper on the subject: “long QT syndrome accompanied by a seizure episode is often misdiagnosed as primary epilepsy.”

**FDA review indicates its “special interest” in seizures, which are mentioned several times as an area of potential concern**

A reported ICSR of epilepsy is notable given the nonclinical findings and prior reports of epilepsy in the postmarketing period. The serious ICSR of epilepsy concerned a 36-year-old female patient with a prior medical history of epilepsy who experienced increased frequency of seizures after exposure to pitolisant. Pitolisant was discontinued after 2 months of treatment. The outcome of the case is unknown.

Seizures and convulsions are also adverse events of special interest for this application; however, none of these events were reported as serious adverse events in narcolepsy clinical trials. Because seizures and cardiovascular events are of special interest in this development program, the SAE of transient ischemic attack (reported by one patient in the HARMONY III trial) is also notable. A summary of the case narrative is below.

Additional evidence of pitolisant’s liver toxicity is buried in the FDA review, in a brief discussion of a pitolisant phase 1 PK study for Prader-Willi Syndrome. One of eight pediatric patients “experienced hepatic enzyme elevation.” Like other Harmony/Bioprojet PK studies, we can locate no further information on the study much less a paper. The study doesn’t even to have a ClinicalTrials.gov entry, making it impossible to know which enzyme, the dose that triggered it, how long after treatment, or when the study was undertaken.

*FDA review indicated hepatic enzyme elevation in one of eight patients*

**HBS-101-CL-003: Pharmacokinetic Study in Pediatric Patients with PWS**

A total of eight patients completed study HBS-101-CL-003, “An Open-Label, Phase 1 Study to Assess the Steady State Pharmacokinetics of Pitolisant in a Predefined Population of Pediatric Patients with Prader-Willi Syndrome.” TEAEs of nasopharyngitis (two patients), upper respiratory infection (one patient), and hepatic enzyme increased (one patient) were reported. The patient who experienced hepatic enzyme elevation recovered after an over-the-counter supplement was discontinued.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
Hypereosinophilic syndrome and drug-induced phospholipidosis overlooked by FDA
Throughout our investigation, we consistently observed a pattern where Harmony and Bioprojet are evasive and conceal information, particularly in relation to significant adverse events. The EMA’s safety review – buried on page 76 of a 102 page document - noted a startling safety signal absent in the FDA review – “abnormal levels of eosinophils” in pitolisant patients, affecting 16.1% of those in the treatment arm in the Harmony 1 trial. Four of 32 pitolisant patients (13%) “were described as hypoeosinophilia” (sic – hyper). The paper for the Harmony 1 trial, in the paragraph on adverse events, makes no mention of eosinophils, not even indirectly. The EMA appears to have had access to additional data that the FDA didn’t, and then takes the company’s explanation at face value: “This was not associated with any specific adverse events.” In our experience, companies only conceal data that they’re worried about, and are more forthcoming if it’s as an innocuous as stated.

**EMA review indicated hypoeosinophilia in 13% of pitolisant patients**

In study Harmony I (P07-03) there was a higher proportion of patients in the pitolisant group with abnormal levels of eosinophils compared to placebo and modafinil groups, at V1 (respectively 16.1% vs 6.7% and 6.1%, p-value=0.454) and at V7 (respectively 16.1% vs 6.7% and 0%, p-value=0.027). The four cases with abnormal levels of eosinophils under pitolisant treatment were described as hypoeosinophilia. This was not associated with any specific adverse events.

The brief EMA mention of hyper-eosinophilia contains no information as to how abnormal the eosinophil count was or whether a tissue biopsy accompanied the blood panel to measure tissue infiltration – “hypereosinophilia is often but not uniformly associated with eosinophilic infiltration of tissues that can potentially lead to irreversible, life-threatening organ damage.” Furthermore, we could locate no mention of hypereosinophilia in any of Bioprojet’s or Harmony’s papers or trials, so we assume they covered it up and/or just stopped measuring it in later studies. Eosinophils are white blood cells that are part of the immune system, typically associated with inflammation. The clinical literature indicates that the lungs are a common target of hypereosinophilic syndrome, and that cardiopulmonary abnormality manifests in >70% of patients.

**Hypereosinophilic syndrome “may intrinsically cause tissue and organ damage”**

Markedly increased blood eosinophilia, ≥1.5 × 10⁹/L, whether discovered fortuitously or found with signs and symptoms of associated organ involvement, commands diagnostic evaluation and often therapeutic interventions. This degree of hypereosinophilia is often, but not uniformly, associated with eosinophilic infiltration of tissues that can potentially lead to irreversible, life-threatening organ damage. Initial approaches focus on ascertaining that eosinophilia is not secondary to other

**Lungs are a frequent target of hypereosinophilia – example papers**

Lung involvement in hypereosinophilic syndromes

Hypereosinophilic syndromes and lung involvement

We are troubled at the lack of any mention of eosinophilic abnormality in the FDA’s review documents. We see two obvious areas of concern, either or both of which may be responsible: 1) off-target effects related to the H4 receptor, and 2) drug-induced phospholipidosis, a known aspect of pitolisant’s toxicity profile, which we get to in a few slides and which has been swept under the rug. Pitolisant targets the H3 receptor, which has low sequence homology with the h1 and h2 receptors which limits off-target effects. However, the H3 and H4 receptors have similar homology, which makes it difficult to target the H3 receptor without also impacting the H4 receptor. The H4 receptor plays a key role in inflammatory reactions and “has been show to activate immune cells such as eosinophils.”

**Paper on role of histamine receptor H4’s “dominant role in histamine-induced eosinophils adhesion...”**

In vitro study of histamine and histamine receptor ligands influence on the adhesion of purified human eosinophils to endothelium

Leukocytes adhesion to endothelial cells is one of the most critical event in the inflammatory response. In presented paper using a relevant model of adhesion we have demonstrated that histamine influence eosinophils adhesion to endothelium. This effect appears to be mediated by H4 histamine receptor, while H1, H2 and H3 histamine receptors are not involved.

**Paper on off-target effects of H3 receptor drugs on the H4 receptor**

Compared pharmacology of human histamine H3 and H4 receptors: structure–activity relationships of histamine derivatives

et al., 2001). The H4R has about 40% sequence homogy to the H3R (58% in transmembrane domains) and both receptors display similar genomic structures with two introns and three exons (Coge et al., 2001b; Tardivel-Lacombe et al., 2001). In
The second paper on the previous slide is by a key scientist in the field, who in 1983 was the first to pharmacologically identify the H3 receptor. He tested a number of compounds (including Bioprojet’s) that target the H3 receptor and showed that they are also generally potent at the H4 receptor, as displayed in the table. He did not test pitolisant. We note that the package insert says that the drug “has no appreciable binding to other histamine receptors,” but the only source appears to be a 2006 preclinical paper by Bioprojet scientist Xavier Ligneau, a member of Schwartz’s inner circle and whose work other scientists have stated is not reproducible in their labs, leading us to take his papers with a grain of salt.

**Paper on off-target effects of H3 receptor drugs on the H4 receptor**

**Compared pharmacology of human histamine H₃ and H₄ receptors: structure–activity relationships of histamine derivatives**

3 The inhibition of [³H]histamine binding by two agonists, a protean agonist and five antagonists/inverse agonists confirms that the potency of many H₃R ligands is retained or only slightly reduced at the H₄R.

**Table 1** Compared potencies of H₃-receptor ligands at the human H₄ and H₃ receptors (H₄Rs and H₃Rs)

<table>
<thead>
<tr>
<th>Agent</th>
<th>hH₄R</th>
<th>hH₃R</th>
<th>Selectivity (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>4.7±0.3</td>
<td>11±2</td>
<td>H₄ (2.3)</td>
</tr>
<tr>
<td>Imetit</td>
<td>1.6±0.1</td>
<td>0.7±0.1</td>
<td>H₃ (2.3)</td>
</tr>
<tr>
<td>Proxyfan</td>
<td>34±1</td>
<td>2.7±0.1</td>
<td>H₃ (13)</td>
</tr>
<tr>
<td>Thioperamide</td>
<td>43±3</td>
<td>60±12</td>
<td>H₄ (1.4)</td>
</tr>
<tr>
<td>Ciproxifan</td>
<td>612±32</td>
<td>46±4</td>
<td>H₃ (13)</td>
</tr>
<tr>
<td>Clobenpropit</td>
<td>4.3±0.2</td>
<td>2.4±0.6</td>
<td>H₃ (1.8)</td>
</tr>
<tr>
<td>FUB 465</td>
<td>704±74</td>
<td>188±12</td>
<td>H₃ (3.7)</td>
</tr>
<tr>
<td>FUB 349</td>
<td>9.5±0.2</td>
<td>2.1±0.2</td>
<td>H₃ (4.5)</td>
</tr>
</tbody>
</table>

As we studied the 13 deaths during the pitolisant development program and the FDA’s database of serious adverse events, the causes and symptoms appear in some cases disparate and were therefore dismissed as unrelated to pitolisant. However, the seemingly unrelated symptoms, notable for an unusual prevalence of pulmonary involvement, share a key trait – they are consistent with hypereosinophilia, which can present as dyspnea, respiratory failure, pulmonary embolism or edema, thromboembolism, cardiac manifestations like cardiomyopathy, fever, rash and allergic reactions, etc. In particular, “cardiac involvement can cause significant morbidity and mortality.”

**Symptoms of hypereosinophilia, per Merck Manual**

**Abnormalities in Patients With Hypereosinophilic Syndrome**

<table>
<thead>
<tr>
<th>System</th>
<th>Prevalence</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>= 50%</td>
<td>Anorexia, fatigue, myalgias, weakness, weight loss</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>&gt; 70%</td>
<td>Mural thrombi with emboli, restrictive or infiltrative cardiomyopathy or mitral or tricuspid regurgitation with cough, dyspnea, heart failure, arrhythmias, endomyocardial disease, pulmonary infiltrates, and pleural effusions</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>&gt; 50%</td>
<td>Angioedema, dermatographism, pruritus, rash (including eczema and urticaria)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>&gt; 50%</td>
<td>Anemia, lymphadenopathy, splenomegaly, thromboembolic phenomena, thrombocytopenia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>&gt; 50%</td>
<td>Cerebral emboli with focal deficits, diffuse encephalopathy with altered behavior and cognitive function and spasticity, peripheral neuropathy</td>
</tr>
</tbody>
</table>

Of the 13 deaths among patients on pitolisant, a large percentage appear remarkably consistent with hypereosinophilia. One patient was hospitalized for bronchopneumopathy (eosinophilic infiltration of the lungs and bronchial mucosa) and died a week later. Another died at home after reporting dyspnea. A third died after being hospitalized for “aspiration and asphyxia” – which appears to be another pulmonary event. A fourth was dead at home due to “acute cardiac and pulmonary insufficiency.” A fifth “went into cardiac and respiratory arrest four days after starting pitolisant.” A sixth died after being hospitalized for “pneumopathy with dysphagia” and “cause of death listed as acute respiratory distress syndrome.”

Table 4 (excerpts): Deaths in the Pitolisant Development Program (All Indications) by 120-Day Safety Update, FDA CDER Clinical Review (Solages, Sep 28, 2020), p10-11

| 58-year-old male with history of obstructive sleep apnea, hypertension, atrial fibrillation, osteoarthritis, obesity, and metabolic syndrome. Found dead at home 2.5 months after the initiation of treatment. No autopsy was performed. Cause of death reported as acute cardiac and pulmonary insufficiency with concomitant severe OSA without continuous positive airway pressure (CPAP). |
| 73-year-old male with Parkinson’s disease. Enrolled in open-label extension for 5 months when hospitalized for bronchopneumopathy. Died 7 days after admission. |
| 80-year-old male with Parkinson’s disease. Enrolled in open-label extension for 9 months when hospitalized for aspiration with asphyxia. Died the day after admission. |
| 64-year-old female with history of pneumonia, hypertension, asthma, chronic obstructive pulmonary disease, and obesity. Went into cardiac and respiratory arrest 4 days after starting pitolisant in open-label extension. No autopsy was performed. Physician diagnosis of stroke per patient’s family. |
| 53-year-old male with history of obstructive sleep apnea, hypertension, type II diabetes mellitus, chronic obstructive pulmonary disease, and obesity. Enrolled in open-label extension for 7 months when died at home after reporting dyspnea and abdominal discomfort. No autopsy. |
| 71-year-old male with Lewy Body Dementia, prior hospitalizations for confusional state and motor deficit, hallucinations, agitation, and aggression. Died 31 days after discontinuing pitolisant in open-label extension phase. Prior to death, had been hospitalized for pneumopathy with dysphagia. Cause of death listed as acute respiratory distress syndrome. |

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
A seventh fatality was due to “pulmonary edema,” a textbook symptom of hypereosinophilia. The FDA’s review exhibited zero awareness of the hypereosinophilia signal and failed to draw any potential link: “No clear association between pitolisant and pulmonary edema is apparent in this narrative.”

**FDA CDER Clinical Review (Solages, Sep 28, 2020), p11-12**

**Patient**

A 61-year-old male patient with a medical history of narcolepsy, sleep apnea, diabetes, hypertension, and overweight died of pulmonary edema. The patient began receiving pitolisant on [redacted], and was receiving a dose of 35.6 mg. The patient’s concomitant medications included venlafaxine, modafinil, clonazepam, metformin, and nebivolol. Death occurred on [redacted]. No autopsy was performed. The Investigator assessed the event as unrelated to pitolisant.

**Reviewer Comment:** Since the original NDA review, two deaths have occurred in pitolisant-treated patients with narcolepsy. The patient who died by suicide had previously experienced a relapse of bipolar disorder symptoms a month after initiating treatment with pitolisant. However, he reportedly recovered from the exacerbation of bipolar symptoms and continued pitolisant treatment without complications for almost 1 year afterwards. The suicide occurred in the context of significant life stressors. The information in the case narrative does not suggest a clear link between pitolisant treatment and the suicide. The second patient died of pulmonary edema. The patient had other co-occurring conditions that could have plausibly increased the risk of developing pulmonary edema. **No clear association between pitolisant and pulmonary edema is apparent in this narrative.**

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
Similarly, neither the FDA nor EMA ever mentioned the risk of drug-induced phospholipidosis, which causes inflammatory reactions – which are of course associated with elevated eosinophils. Pitolisant trials and papers are also radio silent on phospholipidosis. which is highlighted in the literature on H3 receptor antagonists/inverse agonists as a toxicity inherent to the class, particularly drug candidates with a piperidine ring as is the case with pitolisant. Drug-induced phospholipidosis is characterized by the pathological accumulation of phospholipids (fatty molecules) in the tissues, particularly in the lungs given the association of pneumocytes (cells that comprise most of the inner surface of the lungs).

*Research literature on drug-induced phospholipidosis*

**Drug-induced phospholipidosis**

Abstract Drug-induced phospholipidosis is characterized by intracellular accumulation of phospholipids with lamellar bodies, most likely from an impaired phospholipid metabolism of the lysosome. Organs affected by phospholipidosis exhibit inflammatory reactions and histopathological changes. Despite significant

Essentially, drug-induced phospholipidosis is characterized by phospholipid accumulation in affected tissue of which lung, liver, brain, kidney, cornea and others have been reported [3].
The literature on drug-induced phospholipidosis indicates that it is caused by a particular molecular feature shared by certain drugs (“cationic amphiphilic drugs”), and is inherent to H3 receptor antagonist/inverse agonist programs. As noted in a previous section, several pharmaceutical companies with H3R program synthesized pitolisant as part of their research, and specifically noted the drug’s “potential for phospholipidosis” as one of many “important hurdles for this novel compound.”

2008 paper by Abbott researchers indicates they tested pitolisant: “potential for phospholipidosis”

These species. BF2.649 is presently under clinical investigation in several Phase II trials for the treatment of schizophrenia, ADHD, dementia and Parkinson’s disease. (www.stanleyresearch.org/programs/trialgrants.htm). From the development point of view, our laboratory findings suggest that CYP2D6 inhibition, potent hERG binding and the potential for phospholipidosis would likely be important hurdles for this novel compound.

2009 paper indicated phospholipidosis-toxicity for non-imidazole-based H3R compounds like pitolisant

Whilst the majority of non-imidazole classes of H3R antagonists appear not to inhibit significantly the CYP family of enzymes, many H3R antagonist programmes have reportedly suffered from significant blockade of the hERG K⁺ channel [43–45] or have demonstrated the potential for phospholipidosis [43,46] or they have wrestled with P-gp substrate problems. As an example, Abbott’s pre-clinical candidate ABT-239 (Table 1) is reported to exhibit strong binding to the hERG K⁺ channel (Ki = 0.45 nM; 420-fold selectivity H3R/hERG) that manifested itself in a dose-dependent QTc prolongation in dog (Altenbach, personal communication) and monkey [47]. In addition, the compound was also reported to cause phospholipidosis. The combination of these two factors is probably what led to the compound’s demise.
While reviewing papers on drug-induced phospholipidosis, we were struck by one that explained “the seriousness of DIPL” - “the results can be deadly” - by using a case study of a 62-year old woman who was admitted to a hospital “with difficulty breathing.” The condition was incorrectly assessed as bronchitis but was found to be drug-induced. We note the similarity of the narrative to those in the fatalities table for pitolisant trials, where pulmonary involvement is prevalent.

Case study shows respiratory symptoms of drug-induced phospholipidosis

Drug-Induced Phospholipidosis: Best Practices And Screening

Why does phospholipidosis matter?

The seriousness of DIPL can be explained in the case study reported by Gonzalez-Rothi et al. in the 1990s, in which a 62-year old woman was admitted to a Florida hospital with difficulty breathing. Her condition was first misdiagnosed as bronchitis. A year later, with multiple admissions to the hospital, it was identified that her breathing condition was actually the result of phospholipidosis. In her case, it was triggered by the antidepressant fluoxetine hydrochloride (Prozac™) which she had been taking on-and-off throughout the year. DIPL is a reversible process; however, if not caught in time, the results can be deadly.
FAERS database confirms a massive toxicity issue since pitolisant’s approval in 2019, including a recent fatality.
The FDA Adverse Events Reporting System (FAERS) indicates 612 case reports for pitolisant/Wakix through Dec 31, 2022, almost all from 2019 to 2022, despite the relatively small number of patients who have taken the drug. We think lags in the database and/or reporting games by Harmony mean the number of actual case reports in the last two years is several-fold higher, as we shall explain. Of these, 80% (~470 cases) are nervous system and psychiatric and 130 are gastrointestinal. We note 64 respiratory/thoracic and 26 cardiac reports, which are particularly of note given evidence of pitolisant’s cardiotoxicity and the cardiopulmonary-nature of most of the fatalities during clinical trials.

Data and charts from FDA FAERS for search terms Wakix/pitolisant/pitolisant hydrochloride

<table>
<thead>
<tr>
<th>Reaction Group Age Group</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cases</td>
<td>612</td>
</tr>
<tr>
<td>General Disorders And Administration</td>
<td>289</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>256</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>213</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>130</td>
</tr>
<tr>
<td>Injury, Poisoning And Procedural Complications</td>
<td>97</td>
</tr>
<tr>
<td>Respiratory, Thoracic And Mediastinal</td>
<td>64</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td>57</td>
</tr>
<tr>
<td>Investigations</td>
<td>53</td>
</tr>
<tr>
<td>Infections And Infestations</td>
<td>44</td>
</tr>
<tr>
<td>Musculoskeletal And Connective Tissue Disorders</td>
<td>42</td>
</tr>
<tr>
<td>Metabolism And Nutrition Disorders</td>
<td>31</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>27</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>26</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>24</td>
</tr>
<tr>
<td>Blood And Lymphatic System Disorders</td>
<td>22</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>17</td>
</tr>
<tr>
<td>Surgical And Medical Procedures</td>
<td>17</td>
</tr>
<tr>
<td>Renal And Urinary Disorders</td>
<td>13</td>
</tr>
<tr>
<td>Ear And Labyrinth Disorders</td>
<td>7</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>6</td>
</tr>
<tr>
<td>Reproductive System And Breast Disorder</td>
<td>4</td>
</tr>
</tbody>
</table>

Source: FDA FAERS database for Wakix; pitolisant; pitolisant hydrochloride
137 of the 612 cases are classified as serious adverse events of which we note one recent (2022) fatality (dizziness/heart attack two weeks after starting the drug and on the first day the dose was titrated to the max 35.6mg); 2 disabled (17 and 52-year old); 2 life-threatening; and 42 hospitalizations. Below we list the large number of serious adverse events which indicate cardiotoxicity – generally requiring hospitalization. We note that dizziness and seizures are among the most common symptoms of QT prolongation. Across both serious and non-serious event reports, we counted 29 that mentioned “dizziness.” Within serious adverse events specifically, per the list below, we note the frequency of events involving cardiac arrest, myocardial infarction, loss of consciousness, QT prolongation, atrial fibrillation, myocarditis, palpitations, vertigo, hypertension, and stroke.

**Serious adverse event reports which contain the following symptoms or combinations of symptoms**

- Myocardial infarction/dizziness – fatal (1)
- Cardiac arrest (1)
- Myocardial infarction/loss of consciousness/cardiac disorder (1)
- Loss of consciousness (1)
- Dizziness/irregular heartbeat/blurry vision (7)
- Hypertension/tachycardia (8)
- Palpitations/chest pain (4)
- Seizure/QT prolongation per ECG/delirium (1)
- Abnormal QT interval per ECG (1)
- Seizure (2)
- Atrial fibrillation (1)
- Pericarditis (1)
- Ischemic stroke (1)
- Myocarditis (1)
- Chest pain/vomiting (1)
- Tachycardia/palpitations/cardiac disorder (1)
- Vertigo/hypertension (1)

Source: Scorpion Capital analysis and estimates based on FDA FAERS database for Wakix; pitolisant; pitolisant hydrochloride
In addition to serious adverse event reports with cardiac symptoms, we note reports of kidney, liver, or pulmonary-related events that were life-threatening and/or required hospitalization: acute kidney injury (42-year old hospitalized with kidney failure); hepatic enzyme elevation; abnormal hepatic function; two reports of hepatic cytolysis, both relatively young patients (37 and 45 years old); and acute hepatitis (18-year old). Pulmonary embolism is mentioned in four reports, and in a fifth in combination with hepatic enzyme elevation. We speculate that the embolisms may be related to pitolisant’s phospholipidosis liability and/or its potential to cause hypereosinophilic syndrome.

**Serious adverse event reports which contain the following symptoms or combinations of symptoms**

- Acute kidney injury (1)
- Hepatic enzyme elevation/pulmonary embolism (1)
- Abnormal hepatic function/pericarditis (1)
- Hepatic cytolisis (2)
- Acute hepatitis (1)
- Pulmonary embolism (4)
The most prevalent serious adverse event reports are psychiatric or neurological, which isn’t surprising as the H3 receptor is predominantly expressed in the central nervous system. We counted 28 that mentioned some combination of psychosis or psychotic disorder, bipolar disorder, mania, screaming/aggression, schizophrenia, suicidal ideation, and/or hallucinations – with the event reports frequently mentioning the outcome as hospitalization. We note four that mention anaphylactic reaction and/or swollen tongue, and four that indicate splenic infarction, which we speculate could be related to the phospholipidosis or hypereosinophilia issue. Other events include spontaneous abortion and withdrawal symptoms – which we find interesting as the drug is marketed as having no dependency issues whatsoever.

**Serious adverse event reports which contain the following symptoms or combinations of symptoms**

Psychotic disorder; bipolar disorder; mania; hypomania; screaming; aggression; schizophrenia; suicidal ideation; hallucinations (28)
Anaphylactic reaction/swollen tongue (4)
Splenic infarction (4)
Inflammation/pneumonia (1)
Tardive dyskinesia (1)
Spontaneous abortion (1)
Vasospasm (1)
Serotonin syndrome (1)
Withdrawal symptoms (2)

Source: Scorpion Capital analysis and estimates based on FDA FAERS database for Wakix; pitolisant; pitolisant hydrochloride
Our analysis of the FDA FAERS database suggests that adverse events have been massively under-reported and are likely to be several-fold higher than the 612 case reports currently listed. The database contains a variety of date fields (event date, initial FDA received date, latest FDA received date, latest manufacturer received date). The summary stats on the site appear to count the number of adverse events by the “latest FDA received date,” which seems to refer to new info received, rather than by the date of the adverse event. When we count the number of cases by the actual date of the event, a different picture emerges: a spike in 2019 and 2020 in the first year after FDA approval, and then a sharp fall in 2021 and 2022. We are uncertain whether the anomaly is due to lags in the FDA uploading the database (a large number of events appear to be appended several years after the report), or whether Harmony may be dragging its feet, or both.

**Adverse events by event date in FDA FAERS database**

![Adverse Events in FDA FAERS Database Counted By "Event Date"](image)

Source: FDA FAERS database for Wakix; pitolisant; pitolisant hydrochloride; Scorpion Capital analysis and estimates; for events where event date field is blank, we used the "initial FDA received date" as a reasonable proxy.
One can correct and estimate the number of actual adverse event reports in 2021 and 2022 using several methods. For example, total revenue in 2019 and 2020 (almost all in 2020) was ~$165MM. Using an average drug price of $150K/year yields ~1,100 patient years on drug with 415 adverse events during that period. A similar estimate across 2021/2022 yields 4,800 patient years, about 4.5X higher, which would imply 1,900 adverse event reports. The 4.5X factor likely overstates the number, as 2019 included patients in the expanded access program who were presumably not counted as revenue, and some of the events occurred in Europe. Nonetheless, despite the imprecise methodology, it would be unusual for the number of case reports to fall sharply in 2021/2022 with patient counts spiking, suggesting the true figure is multiples higher. We see a similar falloff although not as drastic, regarding the 137 of the 602 adverse events that are classified as serious, indicating that those are too likely substantially higher. We note that we are only estimating case reports to the FDA, not the actual number of adverse events, of which only a small fraction are typically reported.

**Serious adverse events by event date in FDA FAERS database**

![Bar chart showing serious adverse events in FDA FAERS Database counted by "Event Date" for the years 2012 to 2022.](chart)

Source: FDA FAERS database for Wakix; pitolisant; pitolisant hydrochloride; Scorpion Capital analysis and estimates; for events where event date field is blank, we used the "initial FDA received date" as a reasonable proxy.
Individual case narratives for serious adverse events are devastating, obtained via FDA FOIA requests.
A 70-year old male experienced a heart attack and died two weeks after starting pitolisant. Patient had just completed a two-week titration phase with 8.9mg the first week and 17.8mg the second week, and died on the first day he was titrated to 35.6mg. “The patient’s wife stated the patient complained of dizziness during the two-week WAKIX titration phase but did not report it to the sleep center or cardiologist.” We note dizziness is a typical symptom of QT prolongation. The family refused an autopsy. “Although the prescribing information for WAKIX identifies a risk of QT prolongation and therefore should be avoided in patients with known QT prolongation,” the cardiologist “did not consider the heart attack to be related to Wakix” and the event was assessed as unrelated to pitolisant due to pre-existing cardiovascular risk factors and concomitant narcolepsy/cataplexy medications such as Adderall, venlaflaxine, and others.

“Myocardial infarction”
“Dizziness”
(full case narrative on next slide)
Case ID: 21248927, Event date: July 26, 2022 (page 2/2)
A 70-year old male experienced a heart attack and died two weeks after starting pitolisant – full case narrative below.

Event/Problem Narrative:
On (b)(6)****, a spontaneous report was received from a physician's assistant, via a company representative, describing a 70-year-old male (DOB:(b)(6)******) who was being treated with WAKIX (pitolisant) for narcolepsy with cataplexy and experienced a heart attack that resulted in death. On 23-Aug-2022, two electrocardiogram (ECG) reports were received as additional information. Treatment with WAKIX was initiated on 26-Jul-2022. At the time of the event on(b) (6)****, the patient had just completed the two-week titration phase of WAKIX treatment per the recommended prescribing guidelines (i.e., 8.9 mg the first week, 17.8 mg the second week, up to a maximum of 35.6 mg starting the third week). He had taken the first 35.6 mg dose of WAKIX on that day. Medical history included narcolepsy with cataplexy, restless leg syndrome, mild central sleep apnea with an apnea hypopnea index (AHI) of 7, aortic stenosis (Feb-2022), non-specific repolarization abnormality on ECG (Feb-2022) and a body mass index (BMI) of 29. The patient had a 30-pack-year smoking history, although he had quit smoking approximately 10 years ago. Surgical history included partial lumbar discectomy (Feb-2022). Concomitant Medications included Adderall XR (extended-release mixed amphetamine salts) 40 mg twice daily, venlafaxine 75 mg PO once daily, pramipexole 1.5 mg in the morning / 2.5 mg in the evening, methylphenidate 10 mg as needed, herbal supplement for high cholesterol (name unknown), and medical marijuana (per wife, but patient did not have a medical card). On 18-Jan-2022, the patient saw a cardiologist to be cleared for spinal surgery. Nuclear stress test results were negative for ischemia. Echocardiogram (ECHO) results revealed aortic stenosis with an aortic valve area measurement of 0.9 cm² (3-4 cm² is considered normal). ECG interpretation results read "Abnormal ECG: sinus rhythm with premature ventricular complexes or fusion complexes, ST and T wave abnormality with a QTcB of 408 msec. Consider anterolateral ischemia." The cardiologist suggested the patient have a cardiac catheterization, but the patient refused as he did not want to postpone back surgery. On an unknown date in (b)(6)******, the patient underwent a partial lumbar discectomy. On 21-Jul-2022, the patient had a follow-up appointment with his cardiologist. The cardiology notes stated history of aortic valve stenosis, abnormal ECG with non-specific repolarization abnormality, and blood pressure controlled. ECG interpretation results read "Abnormal ECG: normal sinus rhythm with incomplete right bundle branch block, and ST and T wave abnormality with QTcB of 437 msec. Consider anterior ischemia." The patient denied chest pain, orthopnea, dyspnea, and palpitations. The cardiologist again recommended the patient have a cardiac catheterization and another ECHO; however, the patient refused the tests a second time. On (b)(6)***** the WAKIX dose was titrated to 35.6 mg/day. The patient's wife stated the patient complained of dizziness during the two-week WAKIX titration phase but did not report it to the sleep center or cardiologist. The patient owned his own business and worked as a laborer. When he did not return home at his usual time, his wife went to the fields where he worked and found him deceased on the ground next to his 4-wheeler. The lights on the 4-wheeler were not turned on, so his wife assumed he had been dead for a while since it was dark out when she arrived. The wife said the patient was blue when she found him. She started cardiopulmonary resuscitation (CPR) which was unsuccessful. According to the patient's wife, the cardiologist believed the patient had a heart attack. She also stated that a staff member from the cardiologist's office told her that the patient's vessels were narrow, "like trying to drink a milk shake with a tiny thin straw." The cardiologist did not consider the heart attack to be related to WAKIX. The patient's family refused an autopsy. Sponsor's Assessment: This case describes a 70-year-old male with a medical history notable for narcolepsy with cataplexy, aortic stenosis, and cardiac repolarization abnormality (ST and T wave abnormality on ECG as a marker of possible anterolateral ischemia) who had a heart attack resulting in death. The patient was on multiple medications including WAKIX for 2 weeks with the dose titrated to 35.6 mg on the day of the event. Although the prescribing information for WAKIX identifies a risk of QT prolongation and therefore should be avoided in patients with known QT prolongation, given the patient's pre-existing cardiac risk factors of non-specific repolarization abnormality (QTcB interval on the two ECGs was less than 450 msec and QT prolongation was not specifically identified by the cardiologist), aortic valve stenosis, and 30-pack-year smoking history, along with concomitant use of amphetamines, which are contraindicated in patients with cardiovascular disease and known to be associated with fatal cardiovascular events, a contributory role of WAKIX is unlikely.
Case ID: 17861258, Event date: 2020
A 57-year old male patient on 17.8mg of pitolisant experienced “seizures and blacking out.” Pitolisant was discontinued and the symptoms resolved. No other information is provided. We note that seizures and fainting are one of the main symptoms of QT prolongation.

Event/Problem Narrative:
On 14-FEB-2020, a spontaneous report was received from a consumer, via a company representative (Case ID: 021420-2048717), regarding a 57-year-old male who was being treated with WAKIX 17.8 MG (pitolisant). On 09-MAY-2022, the Report Type for this case is being revised from spontaneous to solicited since the initial case information originated from a company-sponsored patient support program.# This case is therefore downgraded to Not Reportable in accordance with the applicable regulatory guidance. Medical history and concomitant products were not reported. On an unspecified date, the patient started treatment with WAKIX 17.8 MG at 17.8 mg, via an unreported route of administration, once daily for an unreported indication. On an unspecified date, after starting the product, the patient experienced seizures and blacking out; which the reporter noted “were the same.” As of 14-FEB-2020, treatment with WAKIX was discontinued and the seizures and blacking out were resolved. No additional information was provided.
Case ID: 17510748, Event date: 2020
A male patient of unreported age, on an unreported date after starting pitolisant, “experienced a seizure and treatment with Wakix and ‘all medicine’ was withdrawn.” The case report suggests a potential attempt by the physician’s office to cover up the event. On Jan 30, 2020, an adverse event report was provided by a nurse via company representative. On Feb 30, 2020, additional info was received from “an anonymous non healthcare provider.” On the same date, the physician’s office reported that “the seizure, occurring after starting the product, was ‘not true’ and ‘an error.’”

Event/Problem Narrative:
On 30-JAN-2020, a spontaneous report was received from a nurse, via a company representative, regarding a male of an unreported age who was being treated with WAKIX (pitolisant). On 13-FEB-2020, additional information was received from an anonymous non healthcare provider. Medical history included narcolepsy and seizures. Concomitant products were not reported. On an unreported date, the patient started treatment with WAKIX at an unreported dose, route and frequency of administration, for narcolepsy. On an unspecified date, after starting the product, the patient experienced a seizure and treatment with WAKIX and “all medicine” was withdrawn. As of 30-JAN-2020, the status of the seizure was not reported. No additional information was provided. On 13-FEB-2020, the health care provider’s office reported that the seizure, occurring after starting the product, was “not true” and an “error.” Further information was requested.
Case ID: 17510921, Event date: 2020 (unclear)
A 25-year old male patient experienced heart palpitations and was hospitalized, per information received on a later date. Patient had an EKG and “everything was fine” – the report is imprecise but the statement appears to be from his physician, as the next sentence says “His doctor thought that he might have reflux.” The report suggests a potential attempt by the physician and/or company representative to cover up the event. The report is again imprecise but appears to quote the physician: “The patient felt this was ‘emotional time and that might be why he had his symptoms.’” However, about 3 months after the event was reported, “additional information was received from the patient’s mother. It was learned that the patient was in the hospital…” The report states “the reporter declined proving additional information,” which again appears to refer to the doctor. The length and outcome of hospitalization are not reported.
Case ID: 17208812, Event date: 2018 or 2019 (report is unclear)

A 27-year old female on 35.6mg of pitolisant was hospitalized for 3 days with acute hypertension. Patient recovered after treatment with medication for high blood pressure. The reporter (appears to be a physician) “assessed acute arterial hypertension as serious and the causality with pitolisant as possibly related”; “although the event is confounded by methylphenidate, for which increased blood pressure is labeled, an association with (b)(6) cannot be ruled out and is assessed as possible.” However, the report indicates the patient had been on methylphenidate since 2012.
Case ID: 18277825, Event date: Feb 2020
18 year old male on 36mg. Started pitolisant on Feb 12, 2020 and was hospitalized 3 months later for acute hepatitis and the drug was withdrawn. No outcome or further info is provided but “with no alternative etiology provided in this report and with the assumption that a patient of this age is relatively healthy, the event of hepatitis is assessed as possibly related to WAKIX.”
Case ID: 20840813, Event date: Jan 20, 2022
A 42-year old female was hospitalized for acute kidney failure secondary to acute urinary retention, 37 days after starting pitolisant (18mg). Pitolisant was discontinued the same day and the patient recovered on an unspecified date. “Limited details regarding medical history, concomitant medications and clinical course were provided; however, due to the temporal relationship, a causal role of WAKIX cannot be ruled out.”

Event/Problem Narrative:
On 06-May-2022, information was received from a physician in France, via Bioprojet, describing a 42-year-old female patient who was being treated with WAKIX (pitolisant) and was diagnosed with acute renal failure which met the serious adverse event criterion of hospitalization. Medical history and concomitant medications were not reported. The patient began WAKIX on 14-Dec-2021 for the treatment of narcolepsy with cataplexy. On(b)(6)******the patient experienced acute renal failure secondary to acute urinary retention and was subsequently hospitalized. The WAKIX dose was 18 mg (presumed daily) at the time of the event. The WAKIX was discontinued that same day, on (b)(6)****. The patient fully recovered from the acute renal failure on an unspecified date. No additional information was provided. Sponsor’s Assessment: This report describes a 42-year-old female who experienced acute renal failure secondary to acute urinary retention 37 days after initiating WAKIX for narcolepsy with cataplexy. Limited details regarding medical history, concomitant medications and clinical course were provided; however, due to the temporal relationship, a causal role of WAKIX cannot be ruled out. Cross-reference Bioprojet Case ID No. FR-
Case ID: 21323707, Event date: May 2022

A 45-year old female was diagnosed with hepatic cytolysis 20 days after starting pitolisant. Lab tests for viral causes were negative, suggesting it may be drug-induced. The report notes the lack of info regarding dose, baseline hepatic function, clinical course, or outcome. Nor does it state if the patient was hospitalized. The patient had a complex medical history including “chronic kidney failure,” dialysis, diabetes, pancreatic failure, and narcolepsy. The pitolisant label suggests 17.8mg daily for patients with moderate or severe renal impairment, although the full prescribing information contains a PK chart that shows 5-fold higher plasma levels in patients with severe impairment at the 90% confidence interval. The patient’s medical history is hardly unusual for narcolepsy patients who present with myriad comorbidities such as obesity, diabetes, cardiovascular history, etc. The report notes that the physician thought it was unrelated to pitolisant and continued treatment, while the FDA stated that “based on a temporal association, a contributory role of WAKIX cannot be ruled out.”

Source: FDA FAERS – FOIA Case Report Information
Case ID: 21370166, Event date: July 2022
Fifteen days after the first dose of pitolisant (4.5mg – a fraction of the labeled dose of 35.6mg), a 62-year old female patient was hospitalized with a “life-threatening” pulmonary embolism. Pitolisant was discontinued and the embolism resolved within 13 days. Patient was concomitantly on fluvoxamine, an SSRI which is a potent CYP2D6 inhibitor. As we note in a previous section, drug-drug interactions with CYP2D6 inhibitors can lead plasma levels of pitolisant to spike.
Case ID: 19955229, Event date: 2021

After two weeks on pitolisant, a 71-year old male patient went to the emergency room with 104 degree fever, “explosive diarrhea”, and chills and was hospitalized. Lab tests revealed “elevated liver enzymes” and “elevated bilirubin of unknown etiology” – “however, it was determined that the patient did not have any type of infection.” The patient was discharged and hospitalized again a day later. A CT scan revealed “two pulmonary emboli in the right lower lobe of his lung.” The report suggests that the patient believed that the emboli were associated with pitolisant but that “nobody” believed him. Event was assessed as not related to pitolisant – case report doesn’t provide the rationale.

Event/Problem Narrative:

On 01-OCT-2021 and 07-OCT-2021, a spontaneous report and follow-up information were received from a consumer describing a 71-year-old male who was being treated with WAKIX (pitolisant). Medical history and concomitant medications were not provided. On an unspecified date in SEP-2021, the patient started treatment with WAKIX for narcolepsy without cataplexy. On (b)(6)****, after starting WAKIX and during the second week of titration (dose was 17.8 mg/day at the time), the patient went to the Emergency Room (ER) with complaints of fever of 103.9 degrees Fahrenheit (F), two bouts of explosive diarrhea and chills. The patient was subsequently admitted for further work-up. Laboratory results revealed elevated liver enzymes and bilirubin (values were not provided). Treatment was not provided; however, it was determined that the patient did not have any type of infection. The cause of the elevated liver enzymes and bilirubin were not provided. The patient was discharged to home on (b)(6)****. He reported that he did not receive WAKIX while in the hospital and denied any withdrawal symptoms. On (b)(6)****, the patient returned to the ER with complaints of fever, chills, severe back pain and bilateral flank pain. A Computed Tomography (CT) scan revealed two pulmonary emboli in the right lower lobe of his lung. The patient was readmitted to the hospital and treatment with Eliquis (apixaban) was initiated (dose/frequency not provided). The patient reported that “nobody” (presumed to mean those involved in his care) believed the pulmonary emboli were associated with WAKIX. On (b)(6)****, treatment with WAKIX was resumed at 35.6 mg. 1x/day. On(b)(6)****, the patient was discharged to home. On 07-OCT-2021, the patient reported he was feeling better and improving. Follow-up information has been requested. Sponsor’s Assessment: A 71-year-old male, treated with WAKIX, was hospitalized for a high fever, diarrhea, chills, elevated liver enzymes, and elevated bilirubin of unknown etiology, as infectious etiology was ruled out. The patient was readmitted one day following discharge with severe back pain and bilateral flank pain, at which time a diagnosis of pulmonary emboli was made. Following discharge after his readmission, the events were reported as improving while treatment with WAKIX was resumed. Although precluded by a lack of information regarding medical history and concomitant medication usage, the pulmonary emboli, fever, diarrhea, chills, elevated liver enzymes, elevated bilirubin, and flank and back pain were assessed as not related to WAKIX.
Case ID: 17241759, event date: Dec 2019

40 year old female on 17.8mg, half the maximal dose. After 11 days on drug, patient was hospitalized for mania, psychotic disorder, bipolar disorder, and insomnia. Patient was also on Wellbutrin, a potent CYP2D6 inhibitor, which we suspect may have spiked plasma levels of pitolisant. Patient may have been on half the maximal dose due to potential drug-drug interaction with Wellbutrin, per suggestion on the label, but still ended up in the hospital. No narrative provided.
Case ID: 19164134, Event date: 2021
17 year old female patient on 17.8mg. Four to five weeks after starting pitolisant, patient was hospitalized for a disassociative/bipolar state with anxiety. Patient was treated with risperdone, an anti-psychotic medication. Symptoms persisted for a week after pitolisant was terminated. “Based on the temporal relationship, the known risk of anxiety and bipolar disorder associated with WAKIX, and the improvement of symptoms following discontinuation, a causal association with WAKIX cannot be ruled out.” The sequence of events suggests a potential attempt to conceal the severity of the event, as the initial adverse event report by the physician and company did not appear to mention the patient was hospitalized. However, the patient’s mother “reported that her daughter was in the hospital due to side effects of the medication,” and the physician then confirmed that this was the same patient as “it was not known at the time [of the mother’s report] that this patient was the same case reported by the physician.”

Event/Problem Narrative:
On 30-MAR-2021, a spontaneous report was received from a physician regarding a 17-year-old female who was treated with WAKIX (pitolisant). On 06-APR-2021, additional information was received from the patient’s mother via a company representative, and based on the information, the case was assessed as serious and unexpected. On 13-APR-2021, additional information was received from the physician. Medical history and concomitant medications were not reported. On an unspecified date in 2021, the patient started treatment with WAKIX for the treatment of narcolepsy with cataplexy. The physician reported that 4 to 5 weeks after starting WAKIX, the patient developed either an anxiety episode which was new for her, or what appeared to be a possible dissociation/bipolar-like state. The reporting physician noted that alternatively, since she had a positive response to WAKIX, that a mood disorder state is emerging more obviously with improved energy and less excessive daytime sleepiness. As of 30-MAR-2021, the action taken with WAKIX, and the outcome of the anxiety, dissociation, bipolar-like state, and mood disorder were not reported. No additional information was reported. On (b)(6)****, a patient’s mother reported that her daughter was in the hospital due to side effects of the medication (presumed to be WAKIX 17.8 mg once daily). It was not known at the time that this patient was the same case reported by the physician on 30-MAR-2021. On 13-APR-2021, the physician confirmed this was the same patient. The physician reported that treatment with WAKIX was withdrawn on an unspecified date and the symptoms persisted for more than one week after discontinuing WAKIX. The patient’s symptoms stabilized with treatment, which included risperidone. She was discharged from hospital during the weekend of (b)(6)******. As of 13-APR-2021, the outcome of the events was reported as improved. No additional information was reported. Comment: Four to five weeks after the start of WAKIX for the treatment of narcolepsy with cataplexy, a 17-year-old female developed either an anxiety episode, possible dissociation/bipolar-like state, or symptoms of a mood disorder for which she was hospitalized. The symptoms persisted for more than one week after WAKIX was discontinued but stabilized with treatment, which included risperidone. As of the last report, the patient had been discharged from the hospital and the outcome of the events was reported as improved. Based on the temporal relationship, the known risk of anxiety and bipolar disorder associated with WAKIX, and the improvement of symptoms following discontinuation, a causal association with WAKIX cannot be ruled out. The patient also received treatment with an anti-psychotic following WAKIX discontinuation, likely contributing to the improvement in her symptoms.

Source: FDA FAERS – FOIA Case Report Information
Case ID: 17930672, Event date: 2020
A 45-year old male patient, “around the time WAKIX was titrated to the maximum dose of 35.6 mg once daily (also reported as "when he got up to the full dose"), the patient had a manic episode and went to a psychiatric hospital ER (emergency room), and required inpatient hospitalization for approximately (b)(6) weeks.” The patient also “felt sad, was screaming, very aggressive, and said he felt like he was God.” Patient was also diagnosed with paranoid schizophrenia while in the hospital. Pitolisant was discontinued and the patient “subsequently felt ‘fine’ which was presumed to mean manic episode, aggression, screaming, and sad feeling were resolved.” The report noted that “with a positive dechallenge, a causal association with WAKIX for the events cannot be ruled out.”

Source: FDA FAERS – FOIA Case Report Information
Case ID: 18135725, Event date: 2020 (unclear)
A female patient in her mid-30’s who was being treated with an unknown dose of pitolisant “showed signs of psychosis.” No information was provided as to hospitalization, outcome, time to onset after starting pitolisant. “Given the known risk of psychiatric events including bipolar disorder and depression, an association with WAKIX cannot be ruled out. Follow-up information is being pursued.”

Event/Problem Narrative:
On 30-JUL-2020, a spontaneous report was received from a nurse practitioner via a company representative regarding a female in her mid-30s who was being treated with WAKIX (pitolisant). Medical history and concomitant products were not reported. On an unreported date, the patient started treatment with WAKIX for an unreported indication. On an unspecified date, after starting the product, the patient showed signs of psychosis. As of 30-JUL-2020, the status of treatment with WAKIX and outcome of signs of psychosis were not reported. No additional information was provided. Comment: A female patient in her mid-30s treated with WAKIX (pitolisant) for an unknown duration and indication showed signs of psychosis, not further described. Lack of further information, including medical history, psychiatric history, concomitant medications, treatment duration, and event details, precludes a complete assessment. Given the known risk of psychiatric events including bipolar disorder and depression, an association with WAKIX cannot be ruled out. Follow-up information is being pursued.
Case ID: 18410926, Event date: 2020
A female patient of unknown age was “hospitalized for ‘psychiatric issues,’ aggression and hallucinations while receiving WAKIX.” According to the physician who submitted the report, “the police were called since the patient became violent and was hallucinating.” Pitolisant was withdrawn and the patient was “back to normal.” The patient was also COVID-positive. “With a positive dechallenge, the events of psychiatric issues, aggression, and hallucinations are assessed as possibly related to WAKIX.”

Event/Problem Narrative:
On 07-OCT-2020, a spontaneous report was received from a physician regarding a female patient (age not reported) who was being treated with WAKIX (pitolisant). Medical history and concomitant medications were not reported. On an unspecified date, the patient started treatment with WAKIX for daytime sleepiness associated with narcolepsy. On an unreported date after starting WAKIX, the patient experienced “psychiatric issues” for which she was hospitalized. According to the reporter, the police were called since the patient became violent and was hallucinating. The patient was also COVID positive during this time. WAKIX was withdrawn. Following WAKIX discontinuation she was “back to normal,” presumed to mean psychiatric issues, violence, and hallucinations resolved. As of(b)(6)*****, the patient's COVID status and the status of her hospitalization were not reported. No additional information was provided. Comment: A female patient was hospitalized for “psychiatric issues,” aggression and hallucinations while receiving WAKIX. The patient was also COVID positive during this time. After WAKIX was withdrawn, she recovered. With a positive dechallenge, the events of psychiatric issues, aggression, and hallucinations are assessed as possibly related to WAKIX. COVID positive test result is assessed as unrelated to WAKIX.
A few months after starting pitolisant, a 29-year old female patient experienced anaphylaxis and hives and rash “all over her back and arms,” joint and muscle pain, dizziness (“feeling like she was going to pass out”), and “shortness of breath and fatigue to the point she could not walk around the block.” The patient discontinued pitolisant and “subsequently, the hives, anaphylaxis, rash, joint and muscle pain, dizziness, and shortness of breath resolved… which is supportive of at least a possible association with WAKIX.”

Source: FDA FAERS – FOIA Case Report Information
Case ID: 19382701, Event date: 2021
A female patient of an unknown age and on an unknown dose of pitolisant underwent an allergy skin test consisting of injections in a grid-like pattern on her back and arm. While the skin test was being performed, the patient experienced an anaphylactic reaction that required two EpiPens (epinephrine injections). “The reporting physician noted the reaction was uncharacteristic of allergy skin testing and implicated WAKIX due to its histaminergic activity. As hypersensitivity, including anaphylactic reaction, is a known risk associated with WAKIX, a causal or contributory role of WAKIX cannot be ruled out.”
A few days after starting pitolisant (started treatment on Mar 3, 2020 and discontinued on Mar 7, suggesting the event occurred in between), a 36-year-old female patient experienced mania, migraines, and an anaphylactic reaction “described as swelling and burning of the lips, itching, tongue swelling, chest pain, wheezing, and lost her voice. Patient went to urgent care and was taken by ambulance to an ER. D-dimer test was conducted to check for pulmonary embolism, and “results showed an increase in D-dimer test.” Pitolisant was discontinued and the patient recovered after treatment in the ER with epinephrine and steroids. “In the absence of alternative etiologies, an association with Wakix is possible.”
Case ID: 17849858, Event date: 2020 (unclear)
A 48-year old female patient was hospitalized for mental health issues with depression and/or anxiety, five days after starting pitolisant. Patient also reported “difficulty catching her breath” (dyspnea) and peripheral edema. “Based on the temporal association between event onset and the start of WAKIX, and as the primary inciting events of anxiety and depression are labeled, the subsequent mental health issues and associated dyspnea are assessed as possibly related to WAKIX, which was ongoing as of last report.”

Event/Problem Narrative:

On 04-MAY-2020, a solicited report was received from a consumer via a company representative (Case ID: 050420-R114980) regarding a 48-year-old female who was being treated with WAKIX (pitolisant). On 19-MAY-2020, additional information was received from a consumer via a company representative (Case ID: 051920-R114980) and based on the information received the case was reassessed as serious, unexpected, and possibly related to WAKIX. On 01-JUN-2020, additional information was received from a consumer via a company representative (060120-R114980). Medical history and concomitant products were not reported. On 30-APR-2020, the patient started treatment with WAKIX for an unreported indication. On 04-MAY-2020, after starting the product, the patient's MD (presumed to mean medical doctor) felt she had depression and or anxiety, but she did not yet have a confirmed diagnosis. The MD was going to be prescribing a new medication for the anxiety and depression, but the patient was not sure which medication they would prescribe as it depended on her ultimate diagnosis. On (b)(6)****, it was learned from the patient that she had been hospitalized for "mental health issues" and had not taken the product since 11-MAY-2020. She was restarting the product "now" (relative to 19-MAY-2020). Since her hospitalization, the patient was newly prescribed Vistaril (hydroxyzine pamoate), Toprol XL (metoprolol succinate), and trazodone (routes, doses, frequencies and indications for use were not reported). As of 04-MAY-2020, the statuses of the patient's anxiety and depression were both unknown and as of 19-MAY-2020, the status of the patient's mental health issues was not reported. No additional information is expected, as contact information for the consumer was not provided. On 01-JUN-2020, additional information was received from the patient and it was learned that since 11-MAY-2020, when she started the "full dose" of the product (previously reported as patient was off the medication from 11-MAY-2020 through 18-MAY-2020), the patient noticed extreme swelling in her lower legs and feet which occurred mid-morning and was gone by bedtime. She also had difficulty catching her breath, which she sometimes noticed with her anxiety. The patient was on multiple unspecified medications so she was not sure what "this could be due to." As of 01-JUN-2020, the status treatment with WAKIX and outcomes of extreme leg swelling, difficulty catching her breath, and anxiety were ongoing. No additional information is expected, as contact information for the consumer was not provided. Comment: A 48-year-old female, treated with WAKIX since 30-APR-2020, was hospitalized for mental health issues with depression and/or anxiety since 04-MAY-2020, and had not taken the product since 11-MAY-2020. She was newly prescribed Vistaril, Toprol XL, and trazodone, and the outcome was not reported. More recently reported events include transient lower extremity swelling and difficulty catching her breath which was possibly related to anxiety, all of which were ongoing. Based on the temporal association between event onset and the start of WAKIX, and as the primary inciting events of anxiety and depression are labeled, the subsequent mental health issues and associated dyspnea are assessed as possibly related to WAKIX, which was ongoing as of last report. Peripheral edema is confounded by trazodone and Toprol XL, for which edema and peripheral edema are labeled, respectively and unlikely related to WAKIX.

Source: FDA FAERS – FOIA Case Report Information
Case ID: 18319093, Event date: Sep 2020
53 year old male patient on 36mg, who stated he is a “heath professional” who has been a “clinical trials coordinator.” He experienced a 9 day gap in getting a refill due to a pharmacy error and “suffered continuous, severe, debilitating headaches” with “extreme nausea.” Symptoms improved within a day when Wakix was refilled. Patient stated that “It's important to note that according to all existing medical literature, to date, there are NO EXISTING REPORTS OF ADVERSE EFFECTS UPON SUDDEN DISCONTINUATION OF WAKIX. Because this is a newly released, novel medication, I thought it was important to report this finding directly to the FDA.” (all caps by patient) We note that pitolisant is marketed as not having any withdrawal symptoms.
Case ID: 17401869, Event date: Jan 2020
62 year old female on 17.8mg, half the maximal dose. Started pitolisant on Jan 9, 2020 and was hospitalized 2-3 weeks later. The case narrative is murky and suggests the initial report via the company and/or physician’s office may have tried to downplay or cover-up the seriousness of the event and deflect responsibility, as information was subsequently received directly from the patient who stated “she was in the hospital due to incorrect dosing” and “the representative from the physician’s office subsequently clarified the event stating that ‘the patient was in the hospital (reason not provided) and the hospital incorrectly administered the dose to the patient..’” Patient was re-started on drug but appears to have stopped immediately as “she felt it was not helping her.”

Source: FDA FAERS – FOIA Case Report Information
Unreported case of drug-induced arrhythmia and hospitalization is a striking signal, given n=16 doctor interviews
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. We note the patient did not meet any of the QT-related precautions on the label. He disclosed the risk to his patients - and all but two quickly discontinued.

Large practice with 50 narcolepsy patients; was keen to try it after reading the literature and doing research
“"I've got about, at this point, narcolepsy patients past and present are getting up to about—it came closer to 50-something patients. And the big issue, obviously, is the excessive daytime sleepiness in patients where it's interfering with normal activities and work, things like that. So, of course, Wakix was something that sounded very interesting because the consensus was that this wasn't something that would be addictive or patients wouldn't become dependent on it. And so, you read the studies, you talk to the reps, and everybody's pretty excited about it. Based off of literature, it sounded like it was the next thing in terms of treating this. So, obviously, it was something I came across in literature, and at a meeting, I decided to give it a try. For the most part, I didn't really have any major issues, but when you get patients who have significant cardiac arrhythmia that they could potentially die from and it kind of causes you to maybe pause a little bit and say, hey, maybe more data needs to be collected, and maybe we shouldn't be first in line to jump on the bandwagon and kind of see how things play out. And that was my response to having patients who had experienced long QT syndrome.”. -Neurologist at a large hospital system in a Midwest state

Only two of ten patients left on it due to QT issue with one patient, who was “a clean, healthy patient, no history of any cardiac issues or arrhythmia”
Q: “When did you first prescribe it?
A: “Last year.
Q: “How many patients did you prescribe it to in total since then?
A: “About 10.”
Q: “And how many are still on it?
A: “Two are still on it. The other 8, after having a discussion with them about the cardiac issue, they opted to stop taking it.”
Q: “So, you had a conversation with the patients about the QT prolongation issue, and they decided to not take it anymore?”
A: “That’s right. And this was, obviously, it was presented initially because it’s on the label. It was like, well, you know, there’s a small chance this could potentially happen. As with anything, we kind of looked at it as a very, very small chance, but I always tell the same patients as well that even if the risk of something is 0.01% when it happens to you, it’s 100%. So, your perspective on it kind of differs. Obviously, having a patient in the practice, you have that—even though we’re not certain, you know, like, yeah, we don’t know 100%, but this is a clean, healthy patient, no history of any cardiac issues or arrhythmia.” -Neurologist at a large hospital system in a Midwest state

Source: Scorpion Capital consultation calls with experts
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients (cont’d)

Otherwise healthy 42-year old taken to emergency room within two months of starting Wakix and diagnosed with QT prolongation

Q: “So, what happened with the patient with the QT prolongation?
A: “Like I said, a pretty healthy guy otherwise. He was at dinner with his wife, and all of a sudden, he got diaphoretic, sweaty. Kind of said, I'm not feeling very good, clammy and diaphoretic. His wife happened to be a nurse. And she said, if you don't feel well, let's go home. So, on their way home, he was really just somnolent, not feeling good. They get home, and she happens to have a BP machine at home that also checks heart rate and sats. She checks it and his heart rate is just off, and she's checking his pulse, and it's irregular. And so, she's worried that he's having a heart attack. Obviously, she calls 911. They take him into the hospital, hook him up, and it's clear as day that he's got an arrhythmia, and initially, they thought maybe he was a-fib because his dad had a history of a-fib but upon further review by cardiology and electrophysiologist saw him, and they're like, oh yeah, he's got a long QT. And so, with the family history of a-fib, they're like, well, this is not a-fib. And they were going through all the medicines like that, anything new, medical history. They kind of said, hey, this is a newer medicine that you said. The cardiologist was pretty astute. He kind of looked up the info and said, hey, this medication can actually cause that, and I don't know necessarily that that's what caused it, but certainly something to talk to your neurologist about. So, they work him up. He gets discharged and follows up with me. He's like, hey doc, this is what happened. And then I'm like, whoa, okay. In that case, the first thing is we're going to stop that medicine and see how things play out. So, obviously, we did.”

Q: “And how long had the patient been on Wakix before this event occurred?”
A: “He had been on it for 8 weeks, 2 months.”

Q: “And what was the age of the patient?”
A: “Forty-two. So, needless to say, it caused everybody to pay a little bit more attention.”

Q: “At 42, was the person obese or had other cardiac morbidities? You said the person was otherwise healthy or pretty healthy?”
A: “Yeah, pretty healthy guy. There is, overall, no real medical history. You know, blood pressure's up a little bit, but nothing major. He was taking one antihypertensive, and he was well-controlled on that.”

Q: “So, the patient is only taking one antihypertensive for mild elevated blood pressure, 42, healthy, shows up in the ER with QT prolongation.”
A: “That's right.” -Neurologist at a large hospital system in a Midwest state
No red flags in the patient; two days in the hospital; presented at the ER diaphoretic, somnolent – “going to pass out”

Q: “There are all of these CYP2D6 issues where depending on your genetics, your phenotype, you can have – and what was the ethnicity of the patient?”
A: “He’s a Caucasian patient. To our knowledge, no cytochrome people should use metabolic mitochondrial –”
Q: “And it sounds like you’re a diligent doctor. Did you do a full panel before the drug to check for renal/hepatic impairment, metabolism issues, and all that stuff?”
A: “Right, absolutely. Absolutely. Nothing, no red flags or anything.”
Q: “And so, the patient who had these symptoms went home, and then what happened? What was the chronology? They just didn’t take anything at home? How long did it take for the symptoms to resolve?”
A: “So, the symptoms did resolve. I can’t remember what medicine they got in the hospital. They got something, some kind of antiarrhythmic in the hospital, IV for the two days they were in the hospital, and everything kind of normalized. The patient went home and followed up with a cardiologist.”
Q: “The patient was in the hospital for two days?”
A: “Two days. Obviously, the cardiologists were working this up. They want to blue light everything, so stress test, echo, everything. That ended up being a two-day issue.”
Q: “What did the ER or the cardiologist see that put the patient in the hospital for two days?”
A: “When the patient was still symptomatic, so the patient was still diaphoretic, not feeling good—in addition to checking cardiac enzymes, the patient was hooked up to a - the patient was diaphoretic, felt like he was somnolent, going to pass out—things like that. So, obviously, when they saw the patient in the ER, they had to work it up.”
Q: “So, the patient’s diaphoretic. I had to look that up. That’s excessive sweating.”
A: “Feeling somnolent and lethargic and tired—
Q: “That they could pass out?”
A: “Yeah, when the patient showed up in the emergency room, they checked cardiac enzymes. They had to rule out myocardial infarction. So, EKG, cardiac enzymes. The patient’s long QT just didn’t refer immediately, so the patient was admitted into observation, hooked up to a monitor, so for telemetry monitoring for heart rate and rhythm strip for 24 hours. The cardiologist wanted to get an echocardiogram to make sure the ejection fraction was standard. Basically, what they were trying to rule out was an underlying cardiac issue.” -Neurologist at a large hospital system in a Midwest state

Source: Scorpion Capital consultation calls with experts
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients (cont’d)

*Doc told the Harmony rep; rep was concerned it was a healthy patient – not one who met the cardiovascular/QT prolongation warning on the label*

Q: “Did you talk to the company or sales rep about it?
A: “I did mention it to the sales rep.”

Q: “What did they say?
A: “The sales rep was also kind of a little bit concerned and said, geez, we know it can do this, but one of the things he said was, not in very healthy people, it's usually people who have some other issues going on, but we know it can cause this. So, that was kind of it, and he just kind of said, well, obviously, even if we don't know for sure, that this is what caused it, and I'm hoping the patient is off of the medicine.”. -Neurologist at a large hospital system in a Midwest state
The foreign clinical trials that led to FDA approval were a scam
The foreign clinical trials that led to the approval of pitolisant are a poster child for the weaknesses and loopholes in the FDA’s fast-track approval process, where a far lower standard of evidence is acceptable for a rare indication. The NDA was based on three phase 3 RCT’s: HARMONY 1, HARMONY I-bis, and HARMONY CTP. The first two were pivotal and submitted as evidence of effectiveness for excessive daytime sleepiness (EDS) in adults with narcolepsy, and the third was for cataplexy in patients with narcolepsy. A fourth called HARMONY 3, a longer-term “open-label, naturalistic, prospective” trial, was submitted as supportive evidence for both indications. Harmony’s presentation contains a summary table of the clinical evidence that underpins the drug.

Harmony investor presentation, Nov 2022

**WAKIX® Phase 3 Clinical Development Program**

<table>
<thead>
<tr>
<th>Name of Study Study Design</th>
<th>Number of Patients</th>
<th>Maximum Dose; % at that Dose</th>
<th>Primary Objective</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARMONY 1</td>
<td>N = 95</td>
<td>35.6 mg; 61%</td>
<td>Assess change in Epworth Sleepiness Scale (ESS) score from baseline to final visit</td>
<td>-6.0 for WAKIX compared to -2.9 for placebo (treatment effect -3.1; p=0.022)</td>
</tr>
<tr>
<td>HARMONY I-bis</td>
<td>N = 166</td>
<td>17.8 mg; 76%</td>
<td>Assess change in ESS score from baseline to final visit</td>
<td>-5.0 for WAKIX compared to -2.8 for placebo (treatment effect -2.2; p=0.030)</td>
</tr>
<tr>
<td>HARMONY CTP</td>
<td>N = 106</td>
<td>35.6 mg; 65%</td>
<td>Assess change in Weekly Rate of Cataplexy (WRC)</td>
<td>WRC decreased 75% for WAKIX compared to 38% for placebo (rate ratio 0.51; p&lt;0.0001)</td>
</tr>
<tr>
<td>HARMONY 3</td>
<td>N = 104</td>
<td>35.6 mg; 88%</td>
<td>Long-term safety</td>
<td>Safety/tolerability profile consistent with that seen in the RCTs</td>
</tr>
<tr>
<td>Human Abuse Potential Study</td>
<td>N = 43</td>
<td>35.6 mg &amp; 213.6 mg: phentermine 60 mg (active control)</td>
<td>Assess drug liking</td>
<td>WAKIX demonstrated a statistically significant and clinically relevant reduction in drug liking compared to phentermine (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Source: https://ir.harmonybiosciences.com/static-files/f5315c60-31f1-e4207-aa4f-53bf52dfe54
The Bioprojet/Harmony trials are not credible scientific studies, but rather dishonest attempts to manipulate trial design and data in order to achieve a predetermined outcome and/or drag the results across the finish line, making a mockery of the scientific method, and highlight the abuses as companies like Harmony and their consultants manipulate and game the extraordinary deference the FDA grants applicants under its accelerated approval pathways. We shall go through each trial in turn and illustrate red flags, statistical tricks, and omissions so rampant that the entire exercise - in our opinion - may be considered a scientific fraud. We first note that although the FDA approved the drug in 2019, the trials are ancient and conducted only in foreign jurisdictions – the typical Jeff Aronin playbook which focuses on old, toxic drugs no one else would touch.

Harmony investor presentation, Nov 2022

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Harmony 1 conducted from May 2009 to Jun 2010, in five western European countries
Harmony 1-bis conducted from Oct 2010 to Jul 2012, in Argentina, Hungary, France, Italy, Spain, Finland, Austria, and Germany
Harmony CTP conducted from Apr 2013 to Jan 2015, in Russia, Serbia, Turkey, Ukraine, Bulgaria, Poland, Macedonia, Czech Republic, and Hungary
Harmony 3 conducted from May 2011 to Oct 2013, in France and Hungary

Source: https://ir.harmonybiosciences.com/static-files/f5315c60-3f1e-4207-aa4f-53b5f2d5e54

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A remarkable feature of Bioprojet’s clinical trials is an obvious pattern of failure, followed by attempts at damage control. HARMONY 1 compared pitolisant to placebo or modafinil, a $50/month generic wakefulness-promoting drug that’s typically the first line of treatment. The trial showed that pitolisant was inferior to modafinil in reducing excessive daytime sleepiness (EDS), the primary endpoint, and also inferior in cataplexy. The study claimed pitolisant is slightly superior to placebo, and used that to persuade the FDA that it was still worthy of approval as it’s purportedly safe and not a scheduled substance. The second pivotal trial, HARMONY 1-bis, was an outright debacle and never published. The design was similar to HARMONY 1. Pitolisant failed to show statistically-significant reduction in EDS or cataplexy vs. either placebo or modafinil, and in fact did even worse vs. modafinil than in HARMONY 1.

Harmony 1 trial paper, published 2013 in The Lancet – pitolisant was inferior to modafinil on the primary endpoint of excessive daytime sleepiness as measured by Epworth Sleepiness Scale; final ESS score in pitolisant arm still indicates excessive sleepiness; also inferior on cataplexy reduction

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<th>Pitolisant</th>
<th>Modafinil</th>
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<td>ESS (primary endpoint; change = final−baseline)</td>
<td>18-9 (2-5)</td>
<td>15-6 (4-3)</td>
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In post-hoc analyses, pitolisant was superior to placebo but not non-inferior to modafinil in terms of improvement in cataplexy rate from baseline (table 2, appendix). In other post-hoc analyses, the percentage of responders (with final ESS scores of 10 or lower) also differed between the pitolisant and placebo groups and were similar between pitolisant and modafinil (table 2).

Source: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(13)70225-4/fulltext
After the abysmal results in these two trials, we suspect Bioprojet went into whatever-it-takes mode and conducted HARMONY CTP in countries where - in our opinion - it simply purchased the outcome it needed. While the two previous trials included sleep centers in South America and Hungary, the majority of patients were still enrolled in western Europe. However, CTP appears to have dispensed with western European sleep centers entirely in favor of Russia, Serbia, Turkey, Ukraine, Bulgaria, Poland, Macedonia, Czech Republic, and Hungary. The paper for the trial fails to disclose the distribution of patients by country, and charts buried in an FDA review explain the reticence: 38% of study participants were in Russia, which along with Ukraine, Turkey, Serbia and Hungary comprised ~90%.

**HARMONY CTP patients by country, per FDA CDER Clinical Review**

![Figure 8: Study Participants by Country - HARMONY CTP (P11-05)](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf; Scorpion Capital estimates and analysis)

38% of study patients were in Russia
Harmony’s clinical trials indicate a pattern of cherry-picking “successful” trials and burying the ones that undermine the drug. Of the ones published (HARMONY 1, CTP, and 3), the papers omit key data and we can find no record of an appendix or supplementary package with a full data set. However, those omissions pale next to failed phase 3 trials that are simply concealed. An astute reader may notice that Harmony’s slide - and FDA submissions - show trials called HARMONY 1 and 3, but curiously no HARMONY 2. Our research indicates a HARMONY 2 trial was in fact conducted - only to fail and be buried, with the oddly-named “1-bis” inserted in its place as “2” was taken. We found another failed trial called HARMONY 4, also buried. Neither was part of the FDA package. Thus, HARMONY 1, 1-bis, 2, and 4 were all failures. The only trials that “worked “ were CTP - where they had to find 21 patients in Russia – and Harmony 3, an absurd open-label naturalistic trial that we shall get to. We show below the only available crumbs for HARMONY 2, from a table in the EMA review and ClinicalTrials.gov. The trial planned to enroll 40 patients but was halted midway, in a failed attempt to re-do HARMONY 1, with modafinil as an add-on to pitolisant.

**HARMONY 2 info from table 7 in EMA review; and ClinicalTrials.gov, which states it was Phase 3**

<table>
<thead>
<tr>
<th>07-07</th>
<th>Efficacy on narcolepsy in a pitolisant versus pitsoln add on Modafinil: HARMONY II</th>
<th>Randomized double-blind, parallel group</th>
<th>20mg tablets Dose: 10mg or 20mg or 40mg per day</th>
<th>14 (8M/6F) Repeated doses 8 weeks</th>
<th>Completed (interrupted) II</th>
</tr>
</thead>
</table>

**Efficacy and Safety Study of BF2.649 and BF2.649 Add on Modafinil on Cataplexy in Patients With Narcolepsy (Harmony2)**

The objective of this POC study are firstly to evaluate and compare the efficacy and safety of escalating doses of BF2.649 and BF2.649 add on Modafinil (200 mg/day) on cataplexy attacks, and secondly to evaluate the additive/synergistic effect and safety of the combination of BF2.649 and Modafinil on EDS as assessed by both of objective and subjective measures including ESS, MWT, patients sleep diary.

**History of changes in ClinicalTrials.gov record shows original enrollment of 40**

HARMONY 4 was a debacle similar to HARMONY 2, and also never published. The FDA’s failure to incorporate either trial into its review was a grave error, as they were the most relevant, real-world trials conducted. Unlike the monotherapy pivotal trials upon which approval was based, these two trials evaluated pitolisant as an add-on to either modafinil or sodium oxybate, the two most common first line treatments. Our interviews with 20 physicians indicate that those willing to use pitolisant rarely do so as a standalone or first-line option and more typically as the third or fourth addition to a cocktail including modafinil and/or sodium oxybate. Former sales reps indicate the company’s entire strategy is to market pitolisant as a combo therapy, given questions about its efficacy. Harmony 4 was conducted between Sep 2012 and Aug 2014, with 51 patients and the same primary endpoint as Harmony 1 – reduction in excessive daytime sleepiness (EDS) using the Epworth Sleepiness Scale (ESS). The trial showed no difference between the pitolisant group and placebo in ESS, nor secondary endpoints like reduction in cataplexy, quality of life, or maintenance of wakefulness test (MWT).

HARMONY 4 info from a 2018 review paper; the paper cites unpublished data provided to the French National Authority for Health, which we located and excerpt below right (from French via Google translate)

The last RCT was the P10-01 (Harmony IV) study, a randomized, double-blind, 8-week, placebo-controlled, add-on to sodium oxybate in 48 narcoleptic patients. The study is completed, but data have not been published, although the French National Authority for Health[47] included data from the study in the report of the Commission de la Transparence regarding pitolisant (21 June 2016). The inclusion and exclusion criteria for this study were similar to those of Harmony I and Ibis. The initial dose was 5mg, with a gradual increase up to 40mg/day during the first 5 weeks. The dose had then to be maintained for 1 month. No difference in daytime sleepiness assessed by the ESS (primary endpoint) was found between the two groups; at the end of the study, the mean score decreased by 2.6 points in the pitolisant group and 2.1 points in the placebo group (p=0.595). No differences were found between pitolisant and placebo in addition to sodium oxybate treatment on the secondary endpoints, especially on the MWT, reduction of cataplexy attacks, and quality of life.[47]

8.1.3 HARMONY IV study versus additional placebo

This is an (unpublished) phase III, randomised, double-blind study which compared the efficacy and tolerance of pitolisant to placebo in addition to treatment with sodium oxybate in 48 patients. The inclusion and exclusion criteria for this study were similar to those of the HARMONY I and Ibis studies. The initial pitolisant dose was 5mg and could be increased up to 40mg/day gradually over the first 5 weeks. The dose was then to be maintained for 1 month.

No difference in terms of daytime sleepiness assessed by the Epworth scale (primary endpoint) was demonstrated between the two groups: at the end of the study the mean score had decreased by 2.6 points in the pitolisant group and 2.1 points in the placebo group (p=0.595).

For information, no difference was also demonstrated between pitolisant and placebo in addition to treatment with sodium oxybate on the secondary endpoints, in particular on the maintenance of wakefulness test (MWT test), the reduction of cataplexy attacks or the quality of life.


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The pages ahead will highlight red flags, statistical tricks, and omissions in the principal trials upon which FDA approval was based – HARMONY 1, 1-bis, CTP, and 3. We discuss each trial one by one, but first we summarize the modus operandi and problems common to the pitolisant clinical trials.

1. Only “successful” trials are presented, while failed trials that contradict the results in these are buried – in particular HARMONY 2 and HARMONY 4, which are now nowhere to be found

2. Published papers for trials are missing or rife with flagrant omissions, without the full data set published for a single trial.

3. Trials are conducted in low-quality geographies known to have compliance and fraud problems; Bioprojet appears to have run the trials itself versus using a third-party CRO

4. Unreasonably short trial and timelines of 8 weeks or less, given narcolepsy is a lifelong condition; longer-term data concealed even though collected for far longer than 8 weeks

5. Cherry-picked trial intervals suggestive of curve-fitting and inconsistent intervals and methods for calculating baseline/final values, with one trial at 8 weeks and another cut off at 7 weeks.

6. Fuzzy inclusion criteria where narcolepsy and cataplexy are subjectively defined, suggesting that trials enrolled individuals who simply had excessive daytime sleepiness vs. actual narcoleptics via HLA genotyping or low CSF hypocretin levels.

7. Trials excluded patients with cardiovascular, hepatic, renal, and psychiatric histories, cherry-picking a patient population highly unrepresentative of a real-world clinical setting, as narcoleptics present with high rates of comorbidities such as hypertension, obesity, diabetes, obesity, etc.

8. Low quality primary endpoint using Epworth Sleepiness Scale (ESS) to measure reduction in excessive daytime sleepiness (EDS). ESS is a highly subjective, unvalidated PRO (patient-reported outcome instrument) that has been condemned in the narcolepsy/sleep literature as a junk, unreliable questionnaire.
Summary of red flags common to each trial (cont’d)

9. No histologic endpoints or data is ever presented. Levels of histamine and/or its metabolites were never shown, nor were CSF hypocretin levels, a narcolepsy marker per ICSD diagnostic criteria.

10. EDS reductions per ESS are modest even in trials gamed to show statistical significance vs. placebo, and final levels are still excessive, indicating results are statistically significant but clinically irrelevant.

11. Huge placebo effect across trials; no dose response

12. No combination trials that reflect its real-world use case, as it is almost exclusively used as a 3rd or 4th line drug in a cocktail.

13. Trials expanded midway, typically a sign of a failing trial that’s scrounging for a small signal by expanding the sample size; other shifting goalposts and endpoint and protocol changes, often undisclosed.

14. Flexible dosing that’s all over the place, with doses titrated up or down at each investigators whimsy from 5mg to 40mg.

15. Concomitant medications were allowed, creating a massive confounding factor as patients were generally on cocktails of drugs

16. Statistical tricks and obfuscations such as artificially clustering trial sites after the fact to adjust p-values; incoherent, bespoke statistical methodologies meant to be impenetrable; shifting intervals and methods for calculating baseline and ending parameters; inconsistent statistical choices like geometric means without any justification
We begin with HARMONY 1, a phase 3 RCT that compared pitolisant versus placebo or modafinil. The primary endpoint was change in Epworth Sleepiness Scale (ESS) scores between the pitolisant and placebo groups after 8 weeks of treatment. ESS – the entire foundation of Harmony’s clinical trials and the key “evidence” of its purported efficacy - is a highly unreliable, unvalidated, subjective, patient-reported questionnaire that assesses chances of falling asleep in different settings. The FDA’s review indicated its skittishness at the use of ESS, but allowed it given the exceptional leniency of the accelerated approval pathway and its past use in other trials in the sleep space: “The Division acknowledges the limitations of this endpoint, as it relies on patients to provide hypothetical responses about how they would respond in different situations and is vulnerable to recall bias.” The Epworth Sleep Scale was written in 1990 by a promotional Australian doctor in private practice, who still shills it online.

*The ESS is available for license at www.epworthsleepinessscale.com*
The Epworth Sleepiness Scale is a farce where the potential for bias, inaccuracy, patient confusion, and coached answers is self-evident. It asks patients to score how likely they are to “doze off” using a 4 point scale across eight life situations, which are redundant and poorly defined: “sitting and reading,” “sitting and talking to someone,” “sitting quietly after lunch,” “sitting inactive in a public place.” The scores are summed across the eight situations to yield a single ESS score. The scale is impossible to validate because each trial appears to have its own version with different prompts and grids/layouts, and it is unclear which version(s) were used in Harmony’s trials. Moreover, the trials would have had to translate and then validate the scale across myriad languages in countries where trials were conducted: Russian, Turkish, Ukrainian, Hungarian, Polish, Finnish, Serbian, Czech, French, Italian, Spanish, etc. – effectively impossible.

Sample ESS questionnaire from the “official site” and other renditions in use

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing (0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0</td>
</tr>
<tr>
<td>Watching TV</td>
<td>1</td>
</tr>
<tr>
<td>Sitting, leisure in public place (e.g. a theater or a meeting)</td>
<td>2</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without stopping</td>
<td>3</td>
</tr>
<tr>
<td>Lying down or in the afternoon when circumstances permit</td>
<td>4</td>
</tr>
<tr>
<td>Sitting and talking in someone</td>
<td>5</td>
</tr>
<tr>
<td>Sitting quietly after a meal without alcohol</td>
<td>6</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td>7</td>
</tr>
</tbody>
</table>

Add up your points to get your total score. A score of 10 or greater raises concern: you may need to get more sleep, improve your sleep practices, or seek medical attention as determining why you are sleepy.

© 1990-1997 NR Johns. Used under license.
The sleep study literature condemns the use of the Epworth scale in trials. The Editor-In-Chief of the Journal of Clinical Sleep Medicine, a professor at Harvard Medical School, slammed it - “Abuse of the Epworth Sleepiness Scale.” Others discuss the prevalence of errors: “…patients have difficulty understanding and accurately self-completing the ESS.” Other studies show its poor reliability, high variability, lack of clinical reproducibility, lack of correlation with symptoms of sleepiness, bias by gender and subpopulation, and numerous other problems.

Examples of studies critical of the use of the Epworth Sleepiness Scale

Abuse of the Epworth Sleepiness Scale

A Requiem for the Clinical Use of the Epworth Sleepiness Scale

The Epworth sleepiness scale: Reliably unreliable in a sleep clinic population

least 3 was observed in 60 (56%) of the participants. Our results suggest that the Epworth Sleepiness Scale should not be used in clinical settings to make individual-level comparisons, such as the effect of therapeutic interventions, or to prioritise access to services.

Clinical Reproducibility of the Epworth Sleepiness Scale

Study Objectives: The Epworth Sleepiness Scale (ESS) is widely used as a subjective measure of sleepiness. To our knowledge, no study has evaluated its reproducibility in the clinical setting.

Conclusion: The ESS score is highly variable when administered sequentially to a clinical population being evaluated for a potential sleep-related breathing disorder.

Low test–retest reliability of the Epworth Sleepiness Scale within a substantial short time frame

These results question the usefulness of the ESS, at the very least, in the follow-up procedures for patients and suggest it must be interpreted cautiously in the evaluation of excessive daytime sleepiness.

The absolute ESS reductions in the HARMONY 1 pitolisant arm were underwhelming and still indicated elevated daytime sleepiness. Baseline sleepiness scores in the arm (17.8) were lower than for placebo and modafinil, setting an easier bar. The max possible ESS score is 24 (0-3 score times 8 settings = 24), and 17.8 is at the low end of “severe excessive daytime sleepiness (16-24)” and near what is defined as “moderate excessive (13-15).” The ending score in the pitolisant arm was 12.0 (5.8 point reduction) – still elevated and only 1 point below “moderate excessive.” A 5.8 point reduction is well within what common sense indicates is the margin of error in a crude survey like ESS – the reduction is equal to a patient self-reporting that they went from a “high chance” of “dozing” to a “slight chance” in 3 of 8 settings, with still a high chance in each of the other 5 settings like “sitting and reading” or “watching TV.”

*Harmony 1 trial paper, published 2013 in The Lancet – table of efficacy results with primary endpoint*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Final</th>
<th>Change over trial*</th>
<th>Pitolisant</th>
<th>Final</th>
<th>Change over trial*</th>
<th>Modafinil</th>
<th>Final</th>
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<th>Treatment effect (mean difference [95% CI]; p value)</th>
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<tr>
<td>Baseline ESS</td>
<td>18.9 (2.5)</td>
<td>16.6 (4.3)</td>
<td>-2.3 (4.2)</td>
<td>17.8 (2.5)</td>
<td>12.0 (6.2)</td>
<td>-5.8 (6.2)</td>
<td>18.5 (2.7)</td>
<td>11.6 (6.0)</td>
<td>-6.9 (6.2)</td>
<td>Pitolisant vs placebo (superiority test)</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pitolisant vs modafinil (non-inferiority test)</td>
</tr>
<tr>
<td></td>
<td>0.0-5</td>
<td>0.0-5</td>
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**ESS score interpretation per www.epworthsleepinesssscale.com**

- 0-5 Lower Normal Daytime Sleepiness
- 6-10 Higher Normal Daytime Sleepiness
- 11-12 Mild Excessive Daytime Sleepiness
- 13-15 Moderate Excessive Daytime Sleepiness
- 16-24 Severe Excessive Daytime Sleepiness


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Aside from paltry absolute reductions in ESS, pitolisant performed far worse than modafinil and only modestly better than placebo. ESS reduction in the pitolisant arm was -5.8, modafinil -6.9, placebo -3.4. The large placebo effect is a red flag, indicating the subjective, unreliable patient-reported endpoint, with the placebo group improving consistently every week to week 8. The placebo-adjusted ESS reduction was merely 2.4 points – equivalent to a moderate reduction in self-reported sleepiness in only one of eight “real life” settings.

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<th>Pitolisant vs modafinil (non-inferiority test)</th>
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</thead>
<tbody>
<tr>
<td>-3.0 (-5.6 to -0.4); p=0.024</td>
<td>0.12 (-2.5 to 2.7); p=0.250</td>
<td></td>
</tr>
</tbody>
</table>

Moreover, pitolisant showed no separation from placebo after week 2 - in fact a small reversal in separation. The bulk of the treatment effect in the trial occurred within weeks 2 and 3, contradicting the Wakix label which indicates it may take 8 weeks to achieve an effect. The trial paper fails to disclose ESS scores by week, but the FDA biometrics review includes it as a table. The table shows that at visit 4 (week 2 of treatment), the separation in absolute ESS scores is -3.7 points (13.0 pitolisant minus 16.7 placebo) vs. final separation of -3.6 points after 8 weeks (12.0 pitolisant minus 15.6 placebo) – which means the separation began to reverse. One can also look at the decline in ESS score vs. baseline, which shows a similar pattern: at week 4, the pitolisant reduction is -2.6 vs. placebo (-4.8 vs. -2.2), and the final reduction is -2.4 vs. placebo (-5.8 vs. -3.4).

**FDA biometrics review for pitolisant – HARMONY 1 table of ESS scores by week**

<table>
<thead>
<tr>
<th>ITT (N=94)</th>
<th>PLACEBO (N=30)</th>
<th>BF2649 (N=31)</th>
<th>MODAFINIL (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>N 30</td>
<td>MN ± SD</td>
<td>MN ± SD</td>
</tr>
<tr>
<td></td>
<td>18.1 ± 2.0</td>
<td>31</td>
<td>15.7 ± 4.4</td>
</tr>
<tr>
<td>Visit 2</td>
<td>15</td>
<td>19.6 ± 2.7</td>
<td>17.4 ± 2.2</td>
</tr>
<tr>
<td>Visit 3</td>
<td>30</td>
<td>19.2 ± 2.6</td>
<td>17.6 ± 2.9</td>
</tr>
<tr>
<td>Baseline (BL)*</td>
<td>30</td>
<td>18.9 ± 2.5</td>
<td>17.8 ± 2.5</td>
</tr>
<tr>
<td>Visit 4</td>
<td>30</td>
<td>16.7 ± 4.1</td>
<td>13.0 ± 4.8</td>
</tr>
<tr>
<td>Visit 5</td>
<td>29</td>
<td>15.9 ± 4.1</td>
<td>12.0 ± 5.9</td>
</tr>
<tr>
<td>Visit 6</td>
<td>27</td>
<td>15.1 ± 4.8</td>
<td>11.4 ± 5.5</td>
</tr>
<tr>
<td>Visit 7</td>
<td>25</td>
<td>15.0 ± 4.6</td>
<td>10.7 ± 6.6</td>
</tr>
<tr>
<td>Final(F) **</td>
<td>30</td>
<td>15.6 ± 4.7</td>
<td>11.8 ± 4.1</td>
</tr>
<tr>
<td>Final(F) †</td>
<td>30</td>
<td>15.6 ± 4.7</td>
<td>12.0 ± 6.2</td>
</tr>
</tbody>
</table>

**No separation vs. placebo after weeks 2 and 3 (visits 4 and 5), whether looking at absolute ESS scores or the decline from baseline to final outcome**

Source: Table 10 of Sponsor’s Clinical Study Report (Page 61)

Source: [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000StatR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000StatR.pdf); Scorpion Capital analysis and estimates
We further note troubling discrepancies between ESS scores in the summary data table vs. the all-important chart of ESS scores by week. The values in the table and chart are consistent for baseline and final ESS scores for placebo and modafinil. The chart also correctly shows the baseline score for pitolisant. However, the final score for pitolisant in the table is 12.0, while the chart shows it as ~10.7 (visually estimated) for week 8 (visit 7). If the chart reflected the value in the table, which appears to be the correct one given multiple references in the paper, it would show a quick and sharp reversal of the pitolisant trend after week 3 (visit 5), undermining the results and necessitating data longer than 8 weeks, which the trials clearly try to avoid with the absurdly short duration.

*Harmony 1 trial paper, published 2013 in The Lancet – table of efficacy on primary endpoint vs. chart*

![Graph showing ESS scores](image)

**Figure 3:** Changes in Epworth sleepiness scale (ESS) score
Data points are mean and error bars are SEM.

As clinically immaterial as the small ESS reductions in HARMONY 1 are, it appears Bioprojet had to double to trial size mid-way in order to conjure them. The paper makes no mention of a trial expansion, and is written to represent that the final powering of 110 was pre-specified. However, the history of changes for the trial’s record on ClinicalTrials.gov indicates it originally planned to enroll only 60 patients. Mid-trial study adjustments which expand the sample size are a red flag and predictive of a flop, as they suggest that the study is failing to show statistical significance and using a larger n to fish for a smaller effect. Common sense indicates that if a study is pointing to efficacy, one has no incentive to expand the size and rock the boat. Such protocol changes are particularly damning because they mean the sponsor was getting results and modifying the trial with knowledge of day-to-day data.

**Harmony 1 trial paper makes no mention of trial expansion and makes the n of 100 appear pre-specified**

**Statistical analysis**

We calculated the sample size on the basis of data from previous trials, based on the minimum clinically relevant difference on a final ESS of 3 points, ESS SD of 5, and a coefficient of correlation $r$ (baseline ESS, final ESS) of 0.65. The first test (difference in change of ≥3 points detectable with a power ≥95%) and the second test (non-inferiority margin of 2 points and 80% as minimal power) needed a sample size of 30 patients per group.

**However, the history of changes on ClinicalTrials.gov indicates the trial size doubled midway - excerpt**

**ClinicalTrials.gov archive**

History of Changes for Study: NCT01067222

Efficacy and Safety Study of BF2.649 in the Treatment of Excessive Daytime Sleepiness in Narcolepsy (Harmony1)

Enrollment: 60 [Anticipated] 110 [Actual]

HARMONY 1 and the other pivotal trials allowed concomitant use of a wide range of medications for narcolepsy, cataplexy, and excessive daytime sleepiness, creating a confounding factor that renders the trials flawed and useless. The protocol stated that patients could remain on anti-cataplectic drugs like sodium oxybate or antidepressants. However, anti-cataplectic drugs are also used to treat narcolepsy symptoms like EDS, making any distinction between narcolepsy and cataplexy drugs irrelevant – and 81% of patients in the pitolisant arm (25/31) had a history of cataplexy. The trial paper states that 13 out of 31 pitolisant patients continued to use anti-cataplectic drugs at “stable dosage,” yet the trial had no ability to monitor adherence, time of day, or sequence of medications. A table in the FDA review shows the hodgepodge of confounding medications taken during the trial across all 3 arms – for example, 23% of pitolisant patients remained on anti-depressants vs. only 13% in the placebo group. Shockingly, 10% of pitolisant patients vs. none in the other arms took “other antihistamines,” which is particularly confounding as pitolisant targets a histamine receptor.

**FDA CDER Clinical Review for pitolisant**

Table 11: Concomitant Medications - HARMONY I (P07-03)

<table>
<thead>
<tr>
<th>Concomitant Medication (Class)</th>
<th>Pitolisant</th>
<th>Modafinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTHER ANTIDEPRESSANTS (^1)</td>
<td>22.6%</td>
<td>18.1%</td>
<td>13.3%</td>
</tr>
<tr>
<td>PROPRONIC ACID DERIVATIVES (^2)</td>
<td>22.6%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>ANILIDES (^3)</td>
<td>16.1%</td>
<td>21.2%</td>
<td>13.3%</td>
</tr>
<tr>
<td>GLUCOCORTICOIDS</td>
<td>12.9%</td>
<td>3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) (^4)</td>
<td>12.9%</td>
<td>15.1%</td>
<td>16.7%</td>
</tr>
<tr>
<td>ACE INHIBITORS, PLAIN</td>
<td>9.8%</td>
<td>9%</td>
<td>3.3%</td>
</tr>
<tr>
<td>OTHER ANTIHISTAMINES FOR SYSTEMIC USE</td>
<td>9.8%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PROGESTGENS AND ESTROGENS, FIXED COMBINATIONS</td>
<td>9.8%</td>
<td>0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>BETA BLOCKING AGENTS, SELECTIVE</td>
<td>8.5%</td>
<td>18.1%</td>
<td>6.7%</td>
</tr>
<tr>
<td>FLUOROQUINOLONES</td>
<td>6.5%</td>
<td>0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>OTHER PSYCHOSTIMULANTS AND NOOTROPICS (^5)</td>
<td>6.5%</td>
<td>6%</td>
<td>13.3%</td>
</tr>
<tr>
<td>PROTON PUMP INHIBITORS</td>
<td>6.5%</td>
<td>18.1%</td>
<td>10%</td>
</tr>
<tr>
<td>PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN (^6)</td>
<td>0</td>
<td>30.3%</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

1. Other antidepressants - duloxetine, reboxetine, venlafaxine
2. Propronic acid derivatives - flurbiprofen, ibuprofen
3. Anilides – acetaminophen, thomaprin
4. SSRIs - citalopram, escitalopram, fluoxetine, paroxetine
5. Other psychostimulants and nootropics - piracetam, sodium oxybate
6. Platelet aggregation inhibitors excluding heparin - acetylsalicylic acid, clopidogrel

Comments published in The Lancet in conjunction with the HARMONY 1 paper critiqued the short 8-week duration of the study – “not a trivial limitation” – in addition to noting that a large percentage of patients remained on anti-cataplectic medications, which meant that “the effect of pitolisant on cataplexy could not be assessed.” The author of the letter, a neuroscientist focused on sleep disorders, stated that the trial investigators “reported that trials…in drug-free patients…are ongoing. The results of these trials will clarify whether pitolisant is a novel alternative treatment for narcolepsy.” Whatever statements the author is referring to strike us as fiction, as we are aware of no such trial that enrolled drug-free patients. Each of the principal trials submitted to the FDA as evidence allowed the use of an extensive array of concomitant medications.

Letter critical of HARMONY 1, published commensurately in The Lancet, 2013

These results are interesting. However, the short duration of the study (8 weeks) is not a trivial limitation; this short timeframe does not allow assessment of the tolerance that might develop with long-term use. Another crucial point of the study is the assessment of cataplexy: 35% of patients continued their usual anticyclaplectic medication during the trial, thus the effect of pitolisant on cataplexy could not be fully assessed. The investigators reported that trials assessing the possible anticyclaplectic activity of pitolisant in drug-free patients as well as long-term trials assessing the effects on EDS are ongoing. The results of these trials will clarify whether pitolisant is a novel alternative treatment for narcolepsy.

HARMONY 1 and the other pivotal trials also used a flexible dosing schedule, and failed to show a dose response – another red flag. Patients in the treatment arm could receive 10, 20, or 40 mg of pitolisant. Critically, the paper fails to disclose the number of 31 pitolisant patients by dose, and nor does it show efficacy results on EDS or secondary measures for dosage subgroups. Two tables buried in the EMA review explain why the paper was less than forthcoming. One reveals that 19 patients (61%) had to be titrated to the highest dose (40mg), suggesting lack of efficacy during the first half of the trial. A second table shows that the 8 patients who remained on 20mg had ESS score improvements 70% greater than those on 40mg (-9.1 vs. -5.1). In other words, patients on the higher dose did far worse, and it appears that statistical significance vs. placebo was driven by the tiny 20mg subgroup. The mean final ESS score in the 18-patient 40mg group was 13.4 vs. 15.6 for placebo – that is, the results were not statistically significant for the largest subgroup. Furthermore, this calls into question the chart of ESS scores by week (slide ___), which shows that the largest drop is in weeks 2 and 3 – if true, why were 18 of 31 patients titrated to double the dose after week 3?

Harmony 1 data by dose per EMA review of pitolisant, 2015 – BF2.649 is pitolisant

Statistical tricks and gimmicks are a defining feature of each Bioprojet/Harmony clinical trial. Impenetrable phrases and assumptions are flung with abandon, a black box of statistical jargon and sorcery devoid of details necessary to comprehend or check the calculations. A recurring trick in the trials is what they call “small centres reallocation,” a mysterious post-hoc (after-the-fact) “adjustment” that takes endpoint data by trial site and tosses it into a martini shaker until the desired output spills out. The HARMONY I-bis study was a failure, as we shortly explain, where they tried a post-hoc “centres reallocation” to kick the trial over the finish line, leading both the EMA and FDA to cry foul despite Bioprojet’s attempt to portray it as pre-planned. HARMONY CTP used the same gimmick, which both agencies missed – a buried footnote states the “centre effect” was “suggested” by HARMONY 1, which also employs the same adjustment and was again missed by the FDA – which is significant given their reaction to it in HARMONY 1-bis.

Harmony 1 (top) and CTP (bottom) both use unexplained “centre effect” to adjust the endpoint values

We adjusted final ESS for baseline values for assessment of the primary endpoint using a mixed linear analysis of covariance, assuming absence of treatment-baseline interaction term and accounting for random centre heterogeneity. Baseline ESS was the exposure at fixed dose); the primary efficacy outcome is cataplexy reduction identified as the rate ratio (pitolisant WCR pb/placebo WCR pb) between basal and final periods; the 1-month stable medication period is considered for final outcome assessment; and a centre effect, suggested by a previous study, is taken into account. All the

Footnote 7 in HARMONY CTP mentions HARMONY 1 as the inspiration for the “centres” reallocation, also used in HARMONY 1-bis

The next pivotal RCT after HARMONY 1 was HARMONY 1-bis. It was a flop and never published, but the EMA and FDA review documents contain telling details. The design was similar to HARMONY 1 – 8 weeks duration with pitolisant compared to placebo and modafinil with ESS again as the primary endpoint. Pitolisant showed an irrelevant -2.19 reduction in ESS vs. placebo, which Harmony claimed was statistically significant with p=0.030 – but only after an unplanned post-hoc clustering of “small clinical study centers,” without which the ESS reduction would have been -1.94 and not stat sig (p=0.065). And the daily cataplexy rate on pitolisant actually doubled from 0.84 at baseline to 1.69. Nonetheless, the FDA viewed the trial as evidence of efficacy, once again illustrating the glaring deficiencies of the accelerated approval pathway. The FDA summarized the EMA review which criticized the “artificial” clustering as unplanned, but then simply gave Harmony a free pass: “The Applicant clarified in a response to an information request that the clustering was in fact pre-planned.”

**FDA quotes the EMA’s criticism of HARMONY 1-bis post-hoc analysis as unplanned, but gave a free pass**

Of note, the EMA Public Assessment Report stated that clustering of small clinical study centers was not pre-planned and that results on the primary endpoint would not be significant without clustering of these centers. The Applicant clarified in a response to an information request that the clustering was in fact pre-planned. Further details, as provided in the biometrics review, are as follows:

“According to EMA Public Assessment Report analysis of the primary efficacy data by “artificially clustering” small clinical study centers, the mean ESS decrease with pitolisant showed statistically significant improvement compared to placebo (-2.19; 95% CI (-4.17, -0.22); p = 0.03). The EMA report stated pooling of centers was not pre-planned. In contrast, the SAP which was issued a month (February 13, 2013) before the database lock (March 13, 2013) included an Appendix (see Figure 14 below) to display the random re-allocation of small centers into clusters. Analysis conducted without re-allocation of small study centers showed that pitolisant didn’t demonstrate statistically significant separation from placebo (-1.94; 95% CI (-4.05, 0.07); p = 0.065). In clarifying FDA request, the applicant made clear (April 25, 2019) that the SAP for the study was amended prior to unblinding of the study.”

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
The FDA blithely accepted Harmony’s explanation that the 1-bis Statistical Analysis Plan issued a month before database lock included an appendix to display the clustering, and took at face value that this plan was “amended prior to unblinding of the study.” The FDA then shows the Statistical Analysis Plan in a table, but it is entirely redacted - presumably at Harmony’s request. We are troubled that something so innocuous would be redacted - on top of the fact that the data was never published in a paper - and are curious what Harmony was so worried about. The EMA review makes no mention of this purported pre-specified Statistical Analysis Plan and bluntly states it was “not pre-planned analysis.” If this plan existed, it would have been provided to the EMA as well and the review would have noted it.

**FDA review redacts the entirety of the purported pre-specified Statistical Analysis Plan**

![Figure 14: Pre-Specified Plan for Clustering of Centers - HARMONY I-BIS](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf)
The EMA noted that the clustering was ultimately irrelevant, as even after using it the ESS reduction barely improved from -1.94 to -2.19. Although this drove the p-value from non-stat sig (p=.07) to stat sig (p=.03), the reduction “was clinically not relevant in both analyses.” In contrast, the FDA missed the forest for the trees and used the 1-bis trial along with HARMONY 1 as sufficient to show efficacy in EDS. Even the HARMONY 1 paper as well as the protocol for HARMONY 1-bis stated that the clinically relevant threshold is 3 points, as the EMA repeats: “This difference was not clinically relevant as it was lower than the pre-defined threshold of 3 points.” The FDA’s reviewer’s conclusion – shown below – exhibits no awareness that a 2 point reduction in ESS is a failure:” “HARMONY 1-bis provides confirmatory evidence of pitolisant’s effect on EDS.”

**EMA rejects HARMONY 1-bis EDS score reduction as clinically immaterial**

According to the pre-specified minimal clinically relevant difference in both pivotal studies, pitolisant showed an improvement on the ESS final score compared to placebo only in Harmony I study (-3.3 points), but not in Harmony Ibis (-2.19 points, with small centres re-allocation and -1.94 points with original centres). The effect of clustering did not improve the modest effect of pitolisant on ESS changes (-1.94 versus 2.19) in Harmony Ibis as it was clinically not relevant in both analysis. However, the clustering artificially improved the p value, from non-significant (p=0.07) to significant (p=0.03).

**However, FDA reviewer missed the forest for the trees and viewed it as evidence of efficacy**

**Reviewer comment:** HARMONY I-bis provides confirmatory evidence of pitolisant’s effect on EDS. This study demonstrated efficacy on the primary endpoint, the ESS. However, when results of the MWT, an objective measure of EDS, were analyzed using the statistical test that was prespecified in the analysis plan, the results were not significant. The CGI-C results suggest that pitolisant had a clinically meaningful effect on EDS, though the study did not detect a difference in quality of life scores or overall opinion on treatment in pitolisant-treated patients. No effect on daily rates of cataplexy was found in this study. The lack of effect on cataplexy events could have been related to the lower maximum dose (20 mg) as compared with the dose in HARMONY I and HARMONY CTP (40 mg).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf
The ESS reduction in the pitolisant arm in HARMONY 1-bis was far worse than the already mediocre results in HARMONY 1. The actual reduction vs. placebo was only 1 point, which Bioprojet then tried to inflate via a statistical “method” that made the placebo ESS reduction ~1 point worse and the pitolisant reduction 1.4 points better. The ending ESS scores in both arms were virtually identical at 14+, an elevated score that indicates significant excessive daytime sleepiness.

Moreover, pitolisant was even more inferior to modafinil than in HARMONY 1 (-4.6 vs. -7.8 for modafinil), and once again failed on cataplexy, per the FDA: “no significant difference in the daily cataplexy rate was found among patients in the three treatment groups.” The trial also failed on secondary endpoints like MWT (Maintenance of Wakefulness Test), SART (Sustained Attention Reaction Test), polysomnography parameters, CGI-C (Clinical Global Impression of Change), etc.

Table of weekly EDS scores by arm per FDA biometrics review shows worse results than even HARMONY 1

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000StatR.pdf

A 1 point change in actual ESS scores (left table) vs. placebo magically converted to -2.19 by making placebo look worse and pitolisant look better.
In addition, HARMONY 1-bis displays all the other red flags as HARMONY 1: questionable foreign jurisdictions, with 40% of trial patients in Hungary and Argentina; pitolisant patients continued taking concomitant narcolepsy medications, creating a confounding factor; dose response data is again withheld, even though dosing was all over the place with 24% of patients on 10mg and 63% on 20mg; protocol violations and amendments, such as what appears to be another trial-size expansion, which the EMA review alludes to with no detail.

Foreign trial with 40% of patients in Hungary and Argentina – FDA review

High use of concomitant medications creates a confounding factor – FDA review

No dose response data provided, even though table in EMA review shows highly variable dosing

Table 25: Concomitant Medications - HARMONY 1-bis (P09-15)

<table>
<thead>
<tr>
<th>Concomitant Medication – Class</th>
<th>Pitolisant</th>
<th>Modafinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPRIONIC ACID DERIVATIVES</td>
<td>14.9%</td>
<td>9%</td>
<td>15.1%</td>
</tr>
<tr>
<td>ANILIDES (paracetamol)</td>
<td>7.5%</td>
<td>10.6%</td>
<td>3%</td>
</tr>
<tr>
<td>SALICYLIC ACID AND DERIVATIVES</td>
<td>7.5%</td>
<td>4.5%</td>
<td>3%</td>
</tr>
<tr>
<td>ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES</td>
<td>4.5%</td>
<td>1.5%</td>
<td>3%</td>
</tr>
<tr>
<td>PENICILLINS WITH EXTENDED SPECTRUM</td>
<td>4.5%</td>
<td>1.5%</td>
<td>3%</td>
</tr>
<tr>
<td>BENZODIAZEPINE DERIVATIVES</td>
<td>3%</td>
<td>1.5%</td>
<td>0</td>
</tr>
<tr>
<td>HMG COA REDUCTASE INHIBITORS</td>
<td>3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PSEUDOEPHEDRINE</td>
<td>3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>XANTHINE DERIVATIVES</td>
<td>3%</td>
<td>1.5%</td>
<td>0</td>
</tr>
<tr>
<td>AMIDEX</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0</td>
</tr>
<tr>
<td>PROTON PUMP INHIBITORS</td>
<td>1.5%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>BIGUANIDES</td>
<td>0</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS</td>
<td>0</td>
<td>4.5%</td>
<td>0</td>
</tr>
<tr>
<td>EXPECTORANTS</td>
<td>0</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>SODIUM OXYBATE</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

1. Propionic acid derivatives – desloratadine, dupriphen
2. Acetic acid derivatives – naproxen, diclofenac (non-steroidal anti-inflammatory agents)
3. Benzodiazepine derivatives – bromazepam, diazepam

*No patients in the study received EMA or other antidepressants

Table 13. Summary of stable dose stage [% (%)] in Harmony 1-bis study.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Dose Received</th>
<th>PLACEBO (N=33)</th>
<th>BF2.649 (N=67)</th>
<th>MODAFINIL (N=68)</th>
<th>TOTAL (N=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.0 (0)</td>
<td>5mg 3.0 (2)</td>
<td>10mg 3.1 (2)</td>
<td>2.4 (4)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>15.6 (5)</td>
<td>10mg 23.9 (16)</td>
<td>20mg 26.2 (17)</td>
<td>21.2 (38)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>81.3 (26)</td>
<td>20mg 62.7 (42)</td>
<td>40mg 66.2 (43)</td>
<td>67.7 (111)</td>
<td></td>
</tr>
</tbody>
</table>

The third primary efficacy study after HARMONY 1 and 1-bis was HARMONY CTP. The first two studies were to support an indication for excessive daytime sleepiness in adults with narcolepsy, and CTP was the principal study for an indication of cataplexy in adults with narcolepsy. CTP was an attempt at damage control, as the FDA advised that a claim for anticataplectic activity needs to be substantiated with two adequate and well-controlled studies. Some background helps explains why CTP was critical - Bioprojet submitted HARMONY 1 and CTP in support of cataplexy, but received a Complete Response Letter (CRL) where the agency stated HARMONY 1 was not adequate for the cataplexy endpoint for three reasons as elaborated in the summary below from the FDA biometrics review:

**FDA rejected HARMONY 1 for cataplexy indication for 3 reasons:**

of the cataplexy indication—HARMONY 1 and HARMONY CTP. As noted in the Complete Response Letter, the Agency determined that HARMONY 1 could not be considered as adequate and well-controlled trial for the cataplexy endpoint for the following reasons:

1. Cataplexy was a secondary endpoint in HARMONY 1. There was no prospective plan to control the Type-I error rate for secondary endpoints in this study.
2. The subgroup of interest was defined post hoc based on event(s) that occurred post-randomization, which violates the randomization principle and could lead to invalid conclusions.
3. The statistically significant finding for cataplexy in HARMONY 1 was dependent on how missing values were handled (i.e., missing or zero values were assigned a value of 0.5; if they were excluded from the analysis, the treatment effect was no longer statistically significant).

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000StatR.pdf
The biometrics review provides a chronology of how the FDA reviewer yet again gave Bioprojet a pass despite obvious red flags and accepted HARMONY 1 as a second trial in support of cataplexy along with CTP. Bioprojet requested a face-to-face meeting after the CRL where it “highlighted with apology this inconsistency [that] arose due to statistician error,” stating that the analysis of cataplexy had been pre-specified all along. The reviewer noted that the purportedly pre-specified analysis was actually a different one (“number of cataplexy attacks” vs. “weekly rate of cataplexy”), but sycophancy won the day as Bioprojet “vehemently agreed with the agency about the need to prespecify primary and secondary endpoints.” The reviewer then noted new errors but gave another pass: “sponsor acknowledged the errors and rectified the efficacy tables…this did not change the overall conclusion but took arduous effort from the statistical reviewer to make sure the sponsor presented accurate analysis results.”

**FDA biometrics review (excerpt) provides chronology for how HARMONY 1 went from CRP to being accepted as the second trial in support of the cataplexy indication**

The Applicant requested a Type A Post-Action face to face meeting, for reconsideration of the CRL decision, and the meeting was held on December 12, 2019 to discuss the Applicant’s re-analysis of the clinical data (number of cataplexy attacks) in HARMONY 1 using Poisson regression which was specified in the original SAP (November 28, 2010). It should be emphasized that although the SAP specified Poisson regression to analyze “number of cataplexy attacks”, in all subsequent submissions including the package for Fast Track, Breakthrough and the NDA, the daily rate of cataplexy (DCR) was analyzed differently using geometric means (applying t-test). All results from the t-test were described in the EMA report, clinical study report (CSR) in the NDA submission.

In the meeting the Applicant highlighted with apology this inconsistency arose due to sponsor’s statistician error. Subsequently, the Applicant made the case that, had Poisson regression been used and any post-hoc multiplicity adjustment procedure applied to all the secondary endpoints, then it can be argued a statistically significant cataplexy endpoint (daily cataplexy rate) can be added in the labeling.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000StatR.pdf
At the point that CTP was conducted, Bioprojet was on thin ice and in need of more convincing data – pitolisant barely reduced ESS scores in HARMONY 1 and showed modafinil to be markedly inferior, and failed to show statistical significance in cataplexy in the absence of post-hoc data games. HARMONY 1-bis results were even worse. The CTP trial was Bioprojet’s last shot and Hail Mary. We think they took no chances and picked trial sites in low-quality foreign jurisdictions where they could simply pay for the results they needed. CTP included no Western European countries: 38% of study participants were in Russia, which along with Ukraine, Turkey, Serbia and Hungary comprised ~90% of patients, in addition to Bulgaria, Poland, Macedonia, and the Czech Republic. The paper for the trial fails to disclose the distribution of patients by country, and charts buried in an FDA review explain the reticence:

**HARMONY CTP patients by country, per FDA CDER Clinical Review**

![Pie chart showing patient distribution by country](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf)

- **38% of study patients were in Russia**

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211150Orig2s000MedR.pdf; Scorpion Capital estimates and analysis
Recent studies have sounded warning bells about fraud and integrity issues in foreign trials especially in Eastern Europe, Russia, and other locations which played an oversized role in the pitolisant trials, particularly HARMONY CTP – “results from sites in Russia…cannot be trusted.” FDA Commissioner Robert Califf commented on similar findings published in the New England Journal of Medicine as “disturbing and it’s good to get it published…offshoring for financial reasons is bad because it raises risk of malfeasance.” A Stanford professor published a paper demonstrating that foreign trials are biased to deliver positive results and questioned “how much we can trust clinical evidence from these settings.” Several studies note wholesale fraud in clinical trials conducted in Russia – in one case, trial personnel simply sold the drug in the open market and patients who supposedly were administered it never actually got it.

Studies and articles on fraud/integrity issues in foreign trials, particularly in Russia and Eastern Europe

Serious Questions Raised About Integrity Of International Trials

As clinical trials have become a global enterprise, many observers have become increasingly worried about the integrity of data from certain geographic areas, in particular from Russia and other countries in the former Soviet Union. Now, a new paper published in the New England Journal of Medicine has provided “smoking gun”

A Clinical Trial Torpedoed By Fraud and Incompetence

These numbers back up an earlier article which drew what has to be the most likely conclusion: that a significant number of patients in Russia and Georgia never ever got the drug. The Cardiobrief piece goes further, airing out the speculation that the spironolactone was, in fact, sold off on the open market by trial personnel rather than actually used as intended. That’s the first thought that occurred to me, too - it had to go somewhere, right?

On the surface, conducting HARMONY CTP in Russia, Serbia, etc. seemed to get Bioprojet what they couldn’t from HARMONY 1 and 1-bis: stunning success on the primary endpoint of weekly rate of cataplexies (WRC), declining from 9.2 to 2.3 on pitolisant vs. 7.3 to 4.5 in placebo; and an ESS score reduction of -3.5 vs. placebo, better than the -2.4 in HARMONY 1 and no ESS effect in 1-bis. The sudden turnaround on the cataplexy rate in CTP vs.1-bis disaster is particularly remarkable – the rate of cataplexy in 1-bis actually worsened dramatically in the pitolisant arm (defined as daily rate in that trial vs. weekly in CTP), doubling from 0.84 to 1.69, per a nugget buried in the EMA review. The results strike us as unusually good vs. the previous trials, and the red flags are just as obvious. First, the placebo effect was massive, with a quick 62% reduction in WRC. Second, the bulk of the effect occurred within a week for both pitolisant and placebo. The key chart in the trial paper is highly misleading, using a log scale for the Y-axis to exaggerate separation vs. placebo, as it was minimal after the first two weeks.

*Chart of Weekly Rate of Cataplexy in trial paper for CTP uses a misleading log scale for Y-axis to exaggerate separation vs. placebo; we re-plotted raw data from a table in FDA biometrics review*

Using a linear Y-axis shows bulk of purported treatment effect occurred instantly, with no further separation vs. placebo during final 4-week stable dosing period.
The primary endpoint of Weekly Rate of Cataplexy was highly subjective and based on a patient-reported diary, rendering the data low-quality and questionable. The definition of cataplexy per the protocol was amorphous and open to extensive patient interpretation, particularly given the inclusion of partial cataplexy: “Patients reported in individual diaries all cataplexy attacks defined as sudden and transient episodes (ranging from several seconds to a few minutes) of partial or generalised loss of muscle tone triggered by emotion.” A patient could consider a brief jerk, twitch, blinking, grimace, or an emotional reaction as partial cataplexy, and could easily associate any body sensation as cataplexy during emotional triggers such as laughter, excitement, stress, or anger.

**Foreign trial with 40% of patients in Hungary and Argentina – FDA review**

**Outcome measures**

The primary outcome for this study was the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing (weekly cataplexy rate [WCR]). Patients reported in individual diaries all cataplexy attacks defined as sudden and transient episodes (ranging from several seconds to a few minutes) of partial or generalised loss of muscle tone triggered by emotion. For each patient, we calculated the final weekly cataplexy rate (WCRf) measured during week 4 of stable dose treatment, and the corresponding baseline rate (WCRb) measured during the 2 weeks preceding randomisation. The cataplexy reduction was measured by the ratio $WCR_{fr} = WCR_f / WCR_b$. 

Source: https://pubmed.ncbi.nlm.nih.gov/28129985/
The CTP trial was once again absurdly short with only a 7-week treatment duration, a week shorter than the brief 8 weeks in HARMONY 1 and 1-bis. The unexplained and arbitrary cut-off suggests an attempt to cherry-pick a favorable data interval. In particular, the primary endpoint seems to have been abruptly changed at the end of the trial – a striking red flag. The record history on ClinicalTrials.gov indicates that the original primary outcome measure was weekly cataplexy rate at week 49. The endpoint remained unchanged from the first entry in Feb 2013 to Jul 2015. In the final record update in Aug 2016, the timeframe is modified from week 49 to week 7 – the change occurred more than 18 months after the study ended in Jan 2105.

**History of changes for HARMONY CTP per ClinicalTrials.gov – screenshot excerpts**

Pitolisant to Assess Weekly Frequency of Cataplexy Attacks and EDS in Narcoleptic Patients (HARMONY CTP)

Other red flags in the CTP trial were the same as HARMONY 1 and 1-bis: concomitant use of medications by 41% of pitolisant patients, particularly anti-cataplectic ones like sodium oxybate and anti-depressants; a flexible dosing schedule with major variability (5mg, 10mg, 20mg, or 40mg), with no data on number of patients or results by dose subgroup, except for a revealing sentence in the FDA review that indicated no dose response, as the risk of cataplexy in the 40mg group was significantly higher than with 20mg; statistical tricks such as a geometric mean to measure WRC; a “centre effect” adjustment to the endpoint as in previous trials, a mysterious statistical conversion that is again never explained; and the omission of virtually all data on the ESS endpoint, such as weekly scores vs. placebo.

No dose response per FDA review, similar to HARMONY 1

Dose/Dose Response

The Applicant analyzed the effect of the 20 mg dose compared to placebo and the 40 mg dose compared to placebo in the stable dose period. The relative risk of cataplexy events in the 20 mg dosing group was 0.392 (95% CI [0.270, 0.571]; p < 0.0001) and 0.523 in the 40 mg dosing group (95% CI [0.510, 0.761]; p < 0.0001).

Mysterious “centre effect” adjustment similar to previous trials – trial paper excerpts

WCR during the 4-week stable dosing period was assessed by a mixed model featuring Poisson regression, with treatment as a fixed factor, adjusted for WCR, treatment centre as a random factor, and exposure time as offset variables. In case of overdispersion, a negative binomial regression was used. WCR/placebo WCR(β) between basal and final periods; the 1-month stable medication period is considered for final outcome assessment; and a centre effect, suggested by a previous study is taken into account. All the
Aside from the principal trials – HARMONY 1, 1-bis, and CTP – Bioprojet submitted HARMONY 3, a phase 3 open-label, “naturalistic,” longer-term (12 mo) study which the FDA indicated was not evidence of efficacy (in the absence of a placebo/control arm) and would be only be viewed as supportive safety information. The EMA had previously taken a similar view: “Unbiased conclusions on efficacy from this study could not be drawn (open-label study, no reference therapy, psychostimulant concomitant treatments, association of naive and already treated patients).” However, despite the low bar, the study throws cold water on the results from the pivotal trials, which were only 7 or 8 weeks. Of 102 patients treated with pitolisant, 73 were de novo of which 40% withdrew prematurely due to lack of efficacy and/or adverse events – and almost all (91%) who discontinued did so within 3 months.

**40% of de novo patients and 17% of exposed patients withdrew almost immediately**

Overall, 34 (33.3%) patients prematurely discontinued the trial, mainly during the first 3 months (31/34), including 29 de novo patients (39.7% of this subgroup) and five (17.2%) exposed patients. The most frequently reported reason was a perceived insufficient efficacy in 20 patients (18 de novo patients, two exposed). However, a treatment response was noted in five of them by their ESS score (decrease of at least three points between the inclusion and withdrawal) in spite of perceived ineffectiveness. In addition, 11 patients discontinued for AEs and three for other reasons.

The efficacy data for ESS and cataplexy shown in the HARMONY 3 paper indicates troubling discrepancies. First, the time to maximal effect is 6 months for ESS and 9-12 months for cataplexy, contradicting the results in HARMONY 1 and CTP which showed that the vast majority of the effect is immediate, within the first couple of weeks of treatment. Second, the ESS score reductions by month 3 and thereafter in the ITT group are implausibly high, given the large number of patient withdrawals by that point due to lack of efficacy. We note that the results are inflated to begin with due to selection bias, as the trial switched over patients from the French Compassionate Use Program.

**ESS and cataplexy results contradict time to maximal effect in prior trials and are otherwise implausible**

![Graph showing ESS and cataplexy scores over time](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6802569/pdf/zsz174.pdf)

**Figure 3.** Epworth sleepiness score over 12 months in the total intention-to-treat population, without replacement of missing values. Data are the mean (±SE) and (95% CI) of number of patients (n).

**Figure 5.** Frequency of episodes of generalized and partial cataplexy over time for the whole ITT population. Data are the means (±SE) and (95% CI) in 43 patients with cataplexy who completed the diaries until the 12-month visit.

Even though the ESS reductions shown in HARMONY 3 are implausibly high given the number of efficacy-related withdrawals, they are still far lower than in HARMONY 1, 1-bis, and CTP to the point that they wouldn’t have been statistically significant vs. placebo had this not been a single-arm trial. The mean ESS reduction in HARMONY 3 after 1, 3, 6, and 12 months was -3.37, -4.39, -4.90, and -4.60. In HARMONY 1, the reduction after 1 and 2 months was -6.1 and -5.8 for pitolisant, and -3.4 and -3.4 for placebo. Thus, if we use the 1 month ESS reduction for placebo (-3.4) from HARMONY 1, the HARMONY 3 reduction was inferior (-3.37). HARMONY 3 didn’t provide 2 month data, but if we average months 1 and 3, the ESS reduction (-3.88) is also not significant vs. the 2 month placebo ESS reduction in HARMONY 1 (-3.4). The HARMONY 3 reductions at 3, 6, and 12 months would also not be significant vs. placebo – we note HARMONY 1 showed a large placebo effect that kept improving through the end of the 8 week trial, suggesting it could be even larger at 3, 6, and 12 months.

**HARMONY 3 ESS reductions**

Sleepiness.

The ESS score, assessed at each visit, decreased along the 12-month period (Figure 3). Compared to baseline, the mean score (±SE) decreased from the first month of treatment (-3.37 ± 0.42; n = 93) and continued to decline after 3 (-4.39 ± 0.51) and 6 months (-4.90 ± 0.54). This change occurred at a similar rate in the de novo or previously exposed patients (Figure 4). In the whole patient population who completed the 12-month treatment (n = 68), the mean decrease from baseline in ESS score was -4.6 ± 0.59 at the end of the period (Table 3). With LOCF method applied to the missing data of the whole population (N = 102, i.e. taking into account the patients having left the trial before 12 months), the reduction was -4.0 ± 0.49. The decrease was

**HARMONY 1 ESS reductions**

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<tr>
<th>Placebo</th>
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<th>HFP450 (N=31)</th>
<th>MERAFOXINE (N=33)</th>
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<tr>
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<td>N</td>
<td>MN ± SD</td>
<td>N</td>
</tr>
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<td>20.0 ± 2.2</td>
<td>19</td>
</tr>
<tr>
<td>Visit 2</td>
<td>19</td>
<td>19.0 ± 2.6</td>
<td>18</td>
</tr>
<tr>
<td>Visit 3</td>
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<tr>
<td>Visit 15</td>
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<tr>
<td>Visit 16</td>
<td>7</td>
<td>7.0 ± 0.8</td>
<td>6</td>
</tr>
</tbody>
</table>

HARMONY 3 calls into question the purported ESS reductions in the three principal trials in support of the pitolisant NDA (HARMONY 1, 1-bis, and CTP), as it was an open-label trial with a low bar given the subjective patient-reported ESS questionnaire, yet the ESS reductions were markedly lower than in the pivotal studies. A nugget buried in an appendix of the EMA review is even more damning, as it shows that most patients discontinue the drug. The HARMONY 3 paper states that 40% of de novo patients discontinued within months due to lack of efficacy. Data provided to the EMA – which the FDA never mentions – indicates the discontinuations only accelerate after year one. HARMONY 3 followed patients for 5 years, even though the trial paper (2019) fails to disclose this fact, and nor does it show any data beyond the first year, which we find troubling. The EMA states that of 102 patients at the start of HARMONY 3, 68 (67%) were left at 12 months, and only 44%, 37%, 33%, and 14% at years 2, 3, 4, and 5. The ESS score at the end of year 1 is even lower than that claimed in the trial paper (-3.62 vs. -4.6) – a reduction identical to that in the placebo arm in their previous trials.

*EMA review (Annex 1) indicated massive discontinuation rates, and indicated 12-mo ESS reduction lower than that purported in HARMONY 3 trial paper and no different than placebo reduction in prior trials*

The open-label, long-term Phase III study (HARMONY III) assessed the long term safety of pitolisant in patients suffering from narcolepsy (with or without cataplexy) over 12 months and with an extension of up to 5 years. 102 narcoleptic patients with or without cataplexy were included in the 12 months follow-up period. 68 patients completed the first 12 months period. 45, 38, 34 and 14 patients completed the 2, 3, 4 and 5 year follow-up periods, respectively. The maximal dose received during the study was 36 mg / day in 85% of patients. After 12 months of treatment, improvements in EDS assessed by ESS score of remaining patients is of same magnitude as those observed in the other trials conducted in narcoleptic patients. The decrease in mean ESS score (SD) was -3.62 (4.63) after 1 year. *ESS score reduction lower than -4.6 in trial paper (excerpted in previous slide)*

>The most devastating physician commentary we have ever heard
We conducted interviews with 16 current and former prescribers of Wakix. We consulted a broad, geographically diverse panel across various practice settings, and specifically sought out a number of Harmony’s speakers and highest volume prescribers – we spoke with 6 of the top 10 recipients of payments from Harmony per the CMS OpenPayments database. We summarize the main findings below:

1. There are almost no high volume prescribers of Wakix who are not paid speakers for Harmony, and even they are generally ambivalent about the drug. Some of the highest volume prescribers nationally - in the top ten - bluntly stated it doesn’t work.

2. Wakix has a supernormal patient discontinuation rate of 30-100% - per individual data points from interviews – typically within weeks or months, due to lack of efficacy and/or side effects. Every single physician, including speakers, provided this color.

3. Physicians generally don’t think Wakix has an effect, or at best an incremental one. Some speculated it’s simply a placebo response, with even the highest volume prescribers conveying the tone that “it’s better than nothing.”

4. Essentially every physician – even among its most ardent “fans,” i.e., speakers – uses Wakix as a 3rd or 4th line drug as part of a cocktail, illustrating the widespread perception of its negligible value. Doctors emphasized it is not a monotherapy and that even Wakix reps only promote it as part of a combination.

5. Wakix is a failed drug launch with no buzz or enthusiasm among sleep physicians, with even speakers saying that Harmony’s market opportunity is saturated, with usage peaking in 2022 and little growth remaining in terms of new patient starts or new prescribers.

Source: Scorpion Capital consultation calls with experts
Summary of main findings from physician interviews (cont’d):

6. New patient starts have plummeted, with one prescriber after another – even speakers – describing a fall-off in late 2021 to 2022, and the last 6 months in particular, as they simply ran out of narcoleptics to try it on.

7. Wakix competes in a crowded field and other drugs work better. Physicians universally stated it is no better than standard of care and generics like modafinil. Doctors are far more excited about sodium oxybate (Xyrem, Xywav).

8. Wakix is plagued by adverse effects and extensive drug-drug interactions, which contribute to its high discontinuation rate. Physicians narrated several serious adverse effects, including a hospitalization for long QT syndrome.

9. Harmony’s sales and marketing messaging has created a false sense of safety and complacency among doctors, who appear to ignore the warnings on the label and generally don’t run tests or monitor patients. This dynamic was especially prevalent among its speakers and highest volume prescribers.

10. Wakix has no value proposition from not being a controlled substance.
We summarize the key takeaways from each actual interview here, followed by 1-3 slides with more detail on each physician consultation.

Prescriber #1: KOL who has published 800 papers in the sleep field, works at a large, prominent center in Texas with hundreds of referring physicians. Has only 6-8 patients on Wakix, which is the last resort at the end of a long list of other drugs and not first line; starts with a cheap generics like modafinil or antidepressants instead; Wakix has a high discontinuation rate with half of patients quitting rapidly due to side effects or lack of efficacy – within “a couple of weeks”; “everybody’s getting some side effect,” which are immediate and bad enough to lead them to discontinue rapidly; drug has had no impact on the field with no enthusiasm from doctors – “I don’t hear about it much from my colleagues”; doesn’t know the price of the drug.

Prescriber #2: KOL in Europe at one of the largest sleep/narcolepsy centers on the continent, began prescribing pitolisant right after EMA approval in 2016. Has only 20 patients on Wakix out of 200; >50% discontinuation rate; incremental drug at best and “not a game changer”; “doesn’t change the landscape”; “I’m think I’m not alone in this opinion”; “if I could only have one drug for all my patients… it would not be pitolisant.”

Prescriber #3: Professor of neurology at a large academic center in the midwest with 120 narcolepsy patients. Was initially bullish but quickly soured on Wakix; crowded field and already have other good therapies – “there’s just not a lot pf open running room for Wakix in the setting of narcolepsy”

Prescriber #4: Neurologist and professor at a leading West Coast academic institution renowned in the sleep/narcolepsy field. Has 30-40 narcolepsy patients but only 5 on Wakix; hasn’t started a new patient on it in a year; “I wasn’t getting the best results”; “I heard rumblings out of Europe that it was just an average drug”; feels guilty that he even prescribes it, does so only because the Harmony rep is persistent and comes monthly; 75% discontinuation rate – “they stop within a month or two”; “weakest of all the drugs out there”; third or fourth line treatment; suspects whatever little effect it has is just placebo; “sometimes I scratch my head about why the people that are on it are on it”; “pales” next to Xyrem where it’s “like a wow, like ‘thank you doc, I feel great’.”

Source: Scorpion Capital consultation calls with experts
Summary of key takeaways from each physician interview (cont’d)

Prescriber #5: Neurologist in private practice in New York with 70-80 narcolepsy patients. Has 15-20 patients on Wakix, the most we encountered by a non-speaker for Harmony, of which half have discontinued; third or fourth line medication in a crowded field; doesn’t even think it works and dispenses it just to offer patients something – “I know it doesn’t fully work. It’s just part of the cocktail, and it’s harmless”; reimbursement is “harrowing…it’s a bunch of hurdles”; no buzz in the field and “a lot of doctors think it’s a waste of money”; partner in his practice won’t prescribe it as he doesn’t “think it works at all.”

Prescriber #6: Physician in private and academic practice in Philadelphia, large practice with five sleep doctors but only 5 Wakix patients among them. No new patient starts in 6 months; “I think that this drug is a little ‘meh’; no buzz or enthusiasm among sleep doctors; “I haven’t had a single patient who said, oh my god, this is so much better”; always part of a cocktail – “never been a first line and even the sales rep told me actually they didn’t promote it that way”; reimbursement pressure has “gotten tighter” in the last 6 months.

Prescriber #7: Physician in the New York/CT area who is a speaker and one of Harmony’s highest volume prescribers, scaling patients right away after FDA approval. We note his atypical prescribing patterns and promotionalism versus physicians who are not speakers. Has ~100 active narcolepsy patients and has put a third on Wakix: “I really, really liked what I saw”; “I had no hesitation to use the medicine”; “it works really, really well.” Often uses it as a standalone medication, in contrast to all other doctors we spoke to – including other speakers, who only use it as 3rd or 4th line in a cocktail. However, he stated insurance has recently become onerous to the point it’s turning off prescribers: “it’s been harder…I’ve been writing more letters and appeals…pain in the ass to prescribe”; “the fellows…say…it’s just so much easier to prescribe modafinil.”

Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers and “has played a big role personally” in educating doctors nationally about the drug. “Aggressive” in offering Wakix to every narcoleptic, yet indicated the drug is not “a game changer,” with merely a subtle effect at best and is only “adjunctive” on top of a cocktail of other drugs. Thinks Harmony’s market opportunity is saturated and Wakix growth will be limited from here. States he’s so unconcerned about side effects that he doesn’t run any lab work – “I do not run EKG’s”; “I don’t check lab work” – and that he has no idea how much the drug costs.

Source: Scorpion Capital consultation calls with experts
Summary of key takeaways from each physician interview (cont’d)

Prescriber #9: UK-based neurologist who has advised Harmony and until recently practiced in the US and used Wakix in both settings; long experience with the drug given involvement with the early access program. Now barely uses it with only 2 patients on drug; 80% discontinuation rate within 1-2 months; “failed drug” that never “really took off”; people “reluctant to use it”; last resort drug and “not aware of any high volume prescribers” – only dabbles, as institutions stopped using it; hasn’t come across a single doctor who raves about it. Lack of efficacy, drug-drug interactions, and side effects cause patients to discontinue. Drug-drug interactions are such a huge problem – “it interacts with everything” – that he advised Harmony they need a separate website to alert patients. Asked Harmony for data from the failed HARMONY 2 trial – which was swept under the rug – but was never given it.

Prescriber #10: Neurologist in New York City at a leading medical center with 20 out of 100-120 narcolepsy patients on Wakix. Has now soured – “I was very excited initially based on the mechanism of action” – but has barely put any patient on in the last 6 months. “Pretty high” discontinuation rate – “a lot of patients just don’t want to stay on it.” Competes in “a pretty saturated field” of EDS and cataplexy drug and no better than “the current standard of care” with inexpensive generics like modafinil. Onerous to prescribe given reimbursement pressure and her “staff was spending a lot of time in that regard.”

Prescriber #11: Neurologist in Texas with “one of the largest narcolepsy patient populations in the US” 200 narcolepsy patients total, of which 50 are on Wakix. Has a long history with Harmony, serving as a key trial investigator, adviser, and speaker. One-third of patients discontinue – “most of the time, I don’t think it’s doing anything.” Complacent about the safety and doesn’t do cardiac screening – “I’ve only run an EKG on one such patient”; liver and kidney issues are “not monitored routinely in narcolepsy centers and sleep clinics as a major concern.” However, still exhibited some underlying concern: “I think that’s something that we’re going to have to watch with this medication.” Provided a narrative of a serious psychiatric adverse event in a patient with no existing history, which began 1-2 weeks after starting Wakix and stopped immediately when it was withdrawn – “she had uncontrollable bursts of anger, and she was like, slamming her desk and stomping her feet on the floor...that was a weird one...could have been...very profound...she doesn’t have any psychosis or bipolar or anything.”
Summary of key takeaways from each physician interview (cont’d)

Prescriber #12: Private practice physician in Northern California who is one of Harmony’s main speakers, with ~110 patients on Wakix out of 250 narcolepsy patients total, and stated he’s one of their top 5 prescribers nationally. Doesn’t even think the drug works and not enthusiastic: “…the main drawback is that it doesn’t work or works very little”; “not going to be like a miraculous wonder drug that goes nuts.” Wakix market opportunity is saturated and peaked a year ago; not much growth likely in new patients or new prescribers, even if they get other indications like idiopathic hypersomnolence; got every prescriber they’re going to get. Estimates that top 5 Harmony prescribers nationally could be 5-700 patients – potentially ~30% of the company’s revenue, by our math. Complacent about safety and does no monitoring – “those items are just warnings…you don’t have to do anything.” Says Harmony won’t disclose the drug’s price to doctors and reps are allegedly instructed not to do so.

Prescriber #13: Neurologist in Los Angeles-area who sees 20-50 narcolepsy patients per year. Initially excited to try Wakix and prescribed it to 20 patients but now has zero: “recently I’ve stopped prescribing it because it doesn’t really do anything.” His usage peaked in 2021 – “…and I think I’ve given it a fairly good try…it was very disappointing.” Experienced a 100% patient discontinuation rate and didn’t help a single patient: “nobody wanted to continue…what’s the point, right?”

Prescriber #14: Neurologist and professor at a pre-eminent medical school, medical advisor to Harmony with a long relationship with the company. Large narcolepsy practice with >100 patients but hasn’t used Wakix in more than ~10 patients cumulatively: no better then generics like modafinil; “doesn’t really knock it out of the park”; “can’t think of a single patient where we’ve used Wakix as monotherapy.” Laughed and said he couldn’t say Wakix is any better than a placebo, and thinks competing drugs like oxybate class are stronger.

Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. We note the patient did not meet any of the QT-related precautions on the label. He disclosed the risk to his patients - and all but two quickly discontinued.

Source: Scorpion Capital consultation calls with experts
Summary of key takeaways from each physician interview (cont’d)

Prescriber #16: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. We note the patient did not meet any of the QT-related precautions on the label. He disclosed the risk to his patients - and all but two quickly discontinued.
Prescriber #1: KOL who has published 800 papers in the sleep field, works at a large, prominent center in Texas with hundreds of referring physicians. Has only 6-8 patients on Wakix, which is the last resort at the end of a long list of other drugs and not first line; starts with a cheap generics like modafinil or antidepressants instead; Wakix has a high discontinuation rate with half of patients quitting rapidly due to side effects or lack of efficacy – within “a couple of weeks”; “everybody’s getting some side effect,” which are immediate and bad enough to lead them to discontinue rapidly; drug has had no impact on the field with no enthusiasm from doctors – “I don’t hear about it much from my colleagues”; doesn’t know the price of the drug.

Large center with 300 referring docs but only 6-8 on Wakix after 3 years; started 12-13 total
A: “My department’s got 300 other more junior psychiatrists and faculty members that will refer people to me.”
Q: “When did you first start prescribing Wakix?
A: “Three years ago, maybe.
Q: “How many people in total did you write a prescription for? How many people did you at least try to put on it over that time, roughly?”
A: “At least half a dozen, 6 to 8, not a huge number, going through the other stuff first. If I include the people who sort of only took it for a week or whatever, then it’s twice as many, so it’s like 12 or 13, that I put on Wakix.” – KOL who has published 800 papers in the field, at a prominent center in Texas

Wakix at the end of a long list of other drugs, not first line; start with modafinil or antidepressants
“The usual sequence for me in terms of prescribing things would be modafinil first, and if that doesn’t work, I may then try either methylphenidate or one of the old tricyclic antidepressants like Anafranil. ...I would go to Xyrem or Xywav because those are more specific and often will work--sometimes Xyrem doesn’t work, in which case, then I would go to Wakix, which is not a first-line drug... I think the most common thing that people usually start with now is modafinil or armodafinil...after modafinil, other things that I’ve used have been methylphenidate, which is a stimulant... And then the usual SSRIs like Prozac, and then it moves on to sort of more specialized drugs. Oxybate, which is gamma-hydroxybutyrate, which is a controlled substance, is the most efficacious, I think. Sodium oxybate.” – KOL who has published 800 papers in the field, at a prominent center in Texas
**Prescriber #1 (cont’d): KOL who has published 800 papers in the sleep field, works at a large, prominent center in Texas**

*Half of patients can quit after “couple of weeks”*

“[B]ecause of this long onset and a particular set of anxiety and insomnia side effects, it’s a drug that you could have half the people just say no thank you after a couple of weeks.” – KOL who has published 800 papers in the field, at a prominent center in Texas

25% get side effects, high drop out rate of 25-50%, “everybody’s” getting “some side effect”

A: “Wakix has a variety of side effects, which include insomnia, nausea, and anxiety, and I would say a quarter or so of people get them, and they just don’t want to take it anymore, particularly since it doesn't act quickly.”

Q: “How many people drop out before the eight weeks, and how many people drop out then because they get side effects?

A: “I would say that I lose about a quarter for side effects and a quarter for— that's a little bit hard to say—the ones that drop out early because it's taking so long, they reason they're dropping out, in part, is because it's got side effects. Everybody's sort of getting some side effect. If they’re getting nausea and anxiety for eight weeks and they're not getting any relief, nobody's going to endure it for that.” – KOL who has published 800 papers in the field, at a prominent center in Texas

**Side effects include insomnia and anxiety – bad enough to discontinue Wakix within a week or days**

Q: “So, those people that tried it two-three times, why did they stop using it so fast? Do they tell you, or you're just not sure?

A: “It's either the insomnia, that’s number one. Number two is the anxiety, and number three is nausea…”

Q: “So, they get those side effects right away, and they're just like, I can't do this more than a couple of days?

A: “Yeah, they get them right from the get-go, and they said the insomnia is probably the worst one because they've already got a sleep disorder, and now they feel that they got two sleep disorders.”

Q: “I see, so it's like a car that can't start, and then all of a sudden, it's like 100 miles an hour with no brakes, basically.

A: “Yeah, they can't sleep at night now, and they're falling asleep during the day, and they say, no wonder I'm falling asleep because I can't sleep at night now either. They feel like I'm making them worse.”

Q: “And how bad are the side effects when they describe them?

A: “It's bad enough so the people won't take the medicine, and that's as bad as you can get.” – KOL who has published 800 papers in the field, at a prominent center in Texas

**No buzz from colleagues at major center in Texas**

Q: “Is this widely prescribed at your institution - what are other people saying to you about it, your colleagues?”

A: “I don’t hear about it much from my colleagues.” – KOL who has published 800 papers in the field, at a prominent center in Texas

**Doesn’t even know the price**

Q: “Do you know how expensive it is?”

A: “Sorry, I don't pay attention to prices that much other than when the patient tells me "I can't afford it" for some reason or other, I have to look for something else.” – KOL who has published 800 papers in the field, at a prominent center in Texas

Source: Scorpion Capital consultation calls with experts
Prescriber #2: KOL in Europe at one of the largest sleep/narcolepsy centers on the continent, began prescribing pitolisant right after EMA approval in 2016. Has only 20 patients on Wakix out of 200; >50% discontinuation rate; incremental drug at best and “not a game changer”; “doesn’t change the landscape”; “I’m think I’m not alone in this opinion”; “if I could only have one drug for all my patients…it would not be pitolisant.”

Only 20 patients on Wakix out of 200
Q: “How many patients of your 200 narcolepsy patients are on pitolisant?"
A: “I think there are 20.” – Physician at one of the largest sleep/narcolepsy centers in Europe, began prescribing pitolisant in 2016/17

>50% discontinuation rate
Q: “How many times have you prescribed it in total, and how many people stayed with it?”
A: “I would say in the past year—only a rough estimate—but perhaps a little more than a half.”
– Physician at one of the largest sleep/narcolepsy centers in Europe, began prescribing pitolisant in 2016/17

Not a game changer; unlikely will work for patients who’ve failed other drugs
“For a patient who did not respond to three or four other anti-narcoleptic drugs, it’s not that there will be such a huge game-changer with pitolisant. In patients who have not responded to previous classical drugs for narcolepsy, it is less probable that pitolisant will completely change the landscape for them.” – Physician at one of the largest sleep/narcolepsy centers in Europe, began prescribing pitolisant n 2016/17

Incremental drug; not the one to choose
“I think it’s just a nice, little additional drug in the whole spectrum of narcolepsy. And this is not, in my opinion, not a big wow…I think I’m not alone in this opinion….if I could only select from all the narcolepsy drugs, so I could only have one drug for all of my patients, I think it would not be pitolisant.” – Physician at one of the largest sleep/narcolepsy centers in Europe, began prescribing pitolisant in 2016/17
Prescriber #3: Professor of neurology at a large academic center in the midwest with 120 narcolepsy patients. Was initially bullish but quickly soured on Wakix; crowded field and already have other good therapies – “there’s just not a lot pf open running room for Wakix in the setting of narcolepsy”

*Was initially bullish but soured; crowded field and already have other good therapies*

“We take care of about 120 people with narcolepsy, the majority of them, probably about 2/3, so 80 are narcolepsy Type 1, and about 40 are narcolepsy Type 2. We have a larger number of idiopathic hypersomnia, happy to discuss as to why that is. But about 200 people with idiopathic hypersomnia. I was quite bullish and excited about a couple of years ago, and I’m less so now. I first became aware of Wakix four years ago…Wakix was always intriguing because it was a novel agent. It was based on histamine, not likely to be addictive, and thus, doesn’t need to FDA elevated schedule. The problem is, especially for narcolepsy, Type 1, we have a lot of good therapies already. There’s just not a lot of open running room for Wakix in the setting of narcolepsy.” – Physician and professor of neurology at a large academic center

Source: Scorpion Capital consultation calls with experts
Prescriber #4: Neurologist and professor at a leading West Coast academic institution renowned in the sleep/narcolepsy field. Has 30-40 narcolepsy patients but only 5 on Wakix; hasn’t started a new patient on it in a year; “I wasn’t getting the best results”; “I heard rumblings out of Europe that it was just an average drug”; feels guilty that he even prescribes it, does so only because the Harmony rep is persistent and comes monthly; 75% discontinuation rate – “they stop within a month or two”; “weakest of all the drugs out there”; third or fourth line treatment; suspects whatever little effect it has is just placebo; “sometimes I scratch my head about why the people that are on it are on it”; “pales” next to Xyrem where it’s “like a wow, like ‘thank you doc, I feel great.”

KOL and professor at a leading academic sleep center hasn’t started a new Wakix patient in a year
A: “I've got about safely 30, probably about 40 narcoleptic patients, which is sky-high. That's probably 10x more than most people.”
Q: “How many patients do you have on pitolisant now?”
A: “My grand total right now is about five out of 40.”
Q: “And was it higher before? Walk me through what your mindset was at the beginning, what changed, and why it’s only five now.”
A: “At the beginning, I was never super-excited by it because I heard rumblings out of Europe that it was just an average drug. So, I never heard that it was an amazing drug, to begin with. I didn’t have super-high expectations. I will say that the patients were excited by it initially. I wasn’t getting the best results…it wasn’t like a wow like they get with Xyrem. For me, the Xyrem is just so effective that it just pales in comparison to that. So, I relegated it pretty early on to my Xyrem failures or Xyrem intolerance… My last start on Wakix was probably late last year or early this year. I can’t recall; it’s been a while, and we’re at the end of this year. It's been almost a year, I have not started anyone.” – Neurologist and professor at a large academic institution

Only prescribe it because rep comes by; most patients discontinue within a month or two
A: “I feel bad saying this - the rep comes every month - and then you think about it, like, okay, I guess I'll try it. And so, then you end up prescribing it a little more because if you don't see them, you forget about it.”
Q: “How many patients have you cumulatively prescribed it to? “
A: “I've written about 15 to 20 scripts overall, over four or five years. Yeah, not that many.”
Q: “Of the patients that you've given it to, the 20 scripts, in total, you have five now. So, did three-quarters of them stop using it?”
A: “Yeah, over time. Most of the ones that stopped, they stopped pretty quickly. They stop within a month or two.”
Q: “And that's because of efficacy or side effects?
A: “Efficacy.” – Neurologist and professor at a large academic institution

Source: Scorpion Capital consultation calls with experts
Prescriber #4 (cont’d): Neurologist and professor at a leading West Coast academic institution renowned in the sleep/narcolepsy field.

*Placebo effect; not sure why patients stay on it; feel guilty that prescribing only because rep is persistent and shows up monthly*

Q: “So you’re using it as a third or fourth-line treatment for somebody who’s a non-responder. So, does it work for non-responder or are you kind of like, I’ve got nothing else, so at least they feel like they have something, maybe they get some placebo benefit?”

A: “Yeah, I think there is **some placebo effect.** Sometimes, I scratch my head about why the people that are on it are on it...**Xyrem is like a wow,** like “Thank you, doc. I feel great.” Even Sunosi, “Whoa, colors are more vivid. Things are clear.” Provigil, eh, it’s okay, but still, it’s easy; it’s generic. So, I think going forward, gosh, **there’s more guilt I feel now, like seeing that rep.**” – Neurologist and professor at a large academic institution

“**Weakest of all the drugs that are out there**”

Q: “It sounds like you don't even think Wakix works. I was going to ask you how long it takes to work, but you don't even know why these patients are taking it.”

A: “…**I think it’s the weakest of all the drugs that are out there.** I think it’s the weakest of all the drugs that will be out there, like compared reboxetine, compared to the Takeda drug.” – Neurologist and professor at a large academic institution
Prescriber #5: Neurologist in private practice in New York with 70-80 narcolepsy patients. Has 15-20 patients on Wakix, the most we encountered by a non-speaker for Harmony, of which half have discontinued; third or fourth line medication in a crowded field; doesn’t even think it works and dispenses it just to offer patients something – “I know it doesn't fully work. It's just part of the cocktail, and it's harmless”; reimbursement is “harrowing…it’s a bunch of hurdles”; no buzz in the field and “a lot of doctors think it’s a waste of money”; partner in his practice won’t prescribe it as he doesn’t “think it works at all.”

Third or fourth line medication in a crowded field

“Wakix has kind of been a crowded field of third-line therapies. First, when we see these patients, we generally step through things like methylphenidate, methamphetamines, etc., like Adderall. We give SNRIs. We'll give Provigil, modafinil if you know what that is—it’s our first line very often. From there, we used to give Xyrem, and now we give Xywav..generally, patients with Type 1 narcolepsy will need to go to third-line in terms of both efficacy and tolerability. There are four FDA-approved medications now for this indication. That’s a lot of options.” -Neurologist in New York with 70-80 narcolepsy patients

Half of patients discontinued within 18 months – 15-20 out of 35-40 starts

A: “I have 15 to 20 patients on Wakix.”
Q: “How many scripts have you written total in the year, year-and-a-half since you've been prescribing the drug – the total number of patients you put on, whether or not they stayed on it. So, the new patient starts in total.”
A: “Altogether maybe I put 35 to 40 patients on it…in general, I do think that we have a good idea of who's staying on the medicine and who's not. But it's an estimation.” -Neurologist in New York with 70-80 narcolepsy patients

Doesn’t even think it works; only used as a cocktail to have something and because assumes it's harmless

Q: “And so, what percentage of the time were you seeing it not work?
A: “Not work is a relative term. I would not say not work enough. In the end, my patients, they're going to be on combination therapy.”
Q: “I guess if Wakix is part of a cocktail, how do you know it works?”
A: “Well, I know it doesn't fully work. It's just part of the cocktail, and it's harmless.” -Neurologist in New York with 70-80 narcolepsy patients

Source: Scorpion Capital consultation calls with experts
Prescriber #5 (cont’d): Neurologist in private practice in New York with 70-80 narcolepsy patients.

No buzz from other doctors who don’t think it works and is a waste of money; partner doesn’t “think it works at all”

Q: “What do you hear from other doctors about it? Is there any buzz about it?
A: “A lot of doctors think it’s a waste of money… I think a lot of doctors are unfamiliar with it or not so excited about it. There’s not so many subscribers of it, and I’m starting to think that some doctors also think that Xywav is it.”

Q: “And what does your partner say about it?”
A: “He doesn’t think it works at all.” -Neurologist in New York with 70-80 narcolepsy patients

Reimbursement makes it a 3rd line drug; hard to get approved

“So, most of the time, I would prefer to use the third-line treatment. They’re just not going to get approved by insurance until I step edits or step through two other treatments…in the end, we get it approved for our patients. But it’s harrowing. It’s a bunch of hurdles.” -Neurologist in New York with 70-80 narcolepsy patients

Source: Scorpion Capital consultation calls with experts
Prescriber #6: Physician in private and academic practice in Philadelphia, large practice with five sleep doctors but only 5 Wakix patients among them. No new patient starts in 6 months; “I think that this drug is a little ‘meh’; no buzz or enthusiasm among sleep doctors; “I haven’t had a single patient who said, oh my god, this is so much better”; always part of a cocktail – “never been a first line and even the sales rep told me actually they didn’t promote it that way”; reimbursement pressure has “gotten tighter” in the last 6 months.

Large practice with 5 docs but only 5 patients on Wakix; “meh” drug; no new starts in 6 months
A: “I’ll just round off and say I have 40 people with narcolepsy, I think maybe 12 of them have cataplexy, and the vast majority don’t… I have about five patients on Wakix….. We have 3 pulmonologists and two neurologists. I even asked the one neurologist. But I can tell you the total number of Wakix among all five of us. It’s not a lot. It’s not as much as these other drugs….”
Q: “When was the last time you had a new patient go on it? So, you’ve had five. When did you last write a script?”
A: “Beginning of the summer, maybe. It may have been six months. Yeah, there has not been a new start…my daughter, I’ll ask - how was Pre-Algebra? She goes, "Meh." Sometimes I think that this drug is a little "meh."” –Physician in private and academic practice in PA with 30-40 narcolepsy patients

No buzz; not a single patient said drug made them “so much better”
Q: “Is there any buzz or enthusiasm among doctors?”
A: “Nah, not really. As I said, I haven’t had a patient who said, oh my god, this is so much better. That’s the one I’m waiting for. I kind of almost want to see the webcast to see what the people who are being paid to do it, who are doctors say in their own experience because I’m just not having that” – Physician in private and academic practice in PA with 30-40 narcolepsy patients

Never been a first line drug; sales rep says only promoted as combo therapy
Q: “What’s the longest you’ve had a patient on Wakix of the five?
A: “Probably two years.
Q: “Is this part of a cocktail, or are they on the drug alone?
A: “It was part of a cocktail, yeah. Usually, with cataplexy, they were on Xywav, and they were on Sunosi, and they were on Wakix, all three, actually. It was step up…I have to say it’s never been a first-line, and even the sales rep told me actually they didn’t promote it that way.”” – Physician in private and academic practice in PA with 30-40 narcolepsy patients
Prescriber #6 (cont’d): Physician in private and academic practice in Philadelphia, large practice with five sleep doctors but only 5 Wakix patients among them.

Insurance become more difficult in last 6 months
A: “It became a little more difficult to prescribe. It required a pre-auth. Usually, you filled out a form, and that was it. And now, there are things like, have you been on modafinil or armodafinil? You have to be on other generics first.”
Q: “And when did you observe this change in the reimbursement climate? Was there a particular point in time?”
A: “Six months ago, probably.”
Q: “So, you think the reimbursement environment has tightened over the last six months?”
A: “Yes. I think over the last year. It seems like it's gotten tighter, yes” - Physician in private and academic practice in PA with 30-40 narcolepsy patients
Prescriber #7: Physician in the New York/CT area who is a speaker and one of Harmony’s highest volume prescribers, scaling patients right away after FDA approval. We note his atypical prescribing patterns and promotionalism versus physicians who are not speakers. Has ~100 active narcolepsy patients and has put a third on Wakix: “I really, really liked what I saw”; “I had no hesitation to use the medicine”; “it works really, really well.” Often uses it as a standalone medication, in contrast to all other doctors we spoke to – including other speakers, who only use it as 3rd or 4th line in a cocktail. However, he stated insurance has recently become onerous to the point it’s turning off prescribers: “it’s been harder…I’ve been writing more letters and appeals…pain in the ass to prescribe”; “the fellows...say...it’s just so much easier to prescribe modafinil.”

1/3 of 90 patients on drug; scaled up prescribing right at approval
A: “At the time, it was marketed as an add-on medicine. It was marketed as if you’re on these three medicines for narcolepsy and you needed a little bit more oomph, try this medicine...I had all these young women, mostly, who were very anxious on their stimulants, their modafinils, their armodafinils, and I thought, great, let’s give it a whirl. So, I got all this early experience early on, and I really, really liked what I saw. So, when it finally got all its FDA approvals, I had no hesitation to use the medicine.”
Q: “You have how many patients on it right now?”
A: “Right now, I’ve got about maybe 90-95 active narcolepsy patients, and so if I’ve got 30, I’ve got roughly a third of them on the medicine...initially, it had this thing around it where it was being marketed as just like an add-on...this is a drug that can be used as a standalone...it works really, really well for both, and maybe even better for cataplexy.”
Q: “When did your use of Wakix scale up?”
A: “It was probably around the time that it got its cataplexy indication. Let’s see, it came out in 2018, maybe, and cataplexy was, I think, 2020. So, probably about 2020.” - Physician in greater New York and CT area

Insurance has become extremely onerous; turns off most doctors
“I know it’s been harder. I’ve been writing more letters and appeals than I have ever done before, but I don’t think that’s because of the cost increases. I think it's just because insurance companies are getting more and more clever at rejecting...That a lot of these medicines are a pain in the ass to prescribe...I mean, it's paperwork, and it’s phone calls, and it's rejections and appeals...I hear what the fellows say. The fellows say that a lot of times that it’s just so much easier to prescribe modafinil or armodafinil. Here, take your stimulant because it's generic, and in all likelihood, it'll be approved. I think docs nowadays, too many docs take the easy way out, and that's how I would explain certain discrepancies...” - Physician greater New York and CT area

Source: Scorpion Capital consultation calls with experts
Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers and “has played a big role personally” in educating doctors nationally about the drug. “Aggressive” in offering Wakix to every narcoleptic, yet indicated the drug is not “a game changer,” with merely a subtle effect at best and is only “adjunctive” on top of a cocktail of other drugs. Thinks Harmony’s market opportunity is saturated and Wakix growth will be limited from here. States he’s so unconcerned about side effects that he doesn’t run any lab work – “I do not run EKG’s”; “I don’t check lab work” – and that he has no idea how much the drug costs.

100 patients on Wakix
“I currently have almost 100 patients on Wakix active… I think we’re probably the largest narcolepsy group anywhere because we only do that.” - Physician and Harmony speaker in Alabama

Most patients are around Huntsville, AL
Q: “Of the hundred patients that you have, how many of them are nearby in Alabama and how many of them telemedicine, just spread out all over the country?”
A: “Oh, there are zero in telemedicine. We have a policy that we don’t write any medications if you live outside a certain radius of our Huntsville practice.”
Q: “I see. So, you have 100 patients on it around Huntsville?”
A: “Oh yeah, oh yeah. Like I said, we attract a lot of narcoleptics.” - Physician and Harmony speaker in Alabama

Claims to be top prescriber in the US
Q: “What has the company told you? Are you one of their—it sounds like you’re one of their most important speakers. I mean, how many other people do they have that have 100 patients on it? Are there a lot of other people like you?”
A: “I don’t know for sure, but, I put a lot of money on the fact that dude, I’m probably their number-one guy. I can’t imagine somebody more aggressive than I am about this. I mean, there might be more people, but I bet you dollars to donuts, I might be the top. I don’t know for sure. I’ve never been told. But, I mean, if I’m not number one, I’ve got to be number two. I mean, there’s no way somebody writes that much more than I do…Who the hell wouldn’t want to write this shit? To me, it blows my mind how doctors don’t write for it. I just can’t figure it out.” - Physician and Harmony speaker in Alabama

Source: Scorpion Capital consultation calls with experts
Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers

Claims to speak frequently for Harmony and has played a key role in educating other doctors
A: “I'm a paid consultant on behalf of several different drug companies for narcolepsy. And when the representative says there's a group in here that really wants a doctor who’s an expert in that drug to come out and give a lecture, then they fly me out if it's far away…”
Q: “And when did you start doing that? When you first got excited about the drug in late 2019?
A: “Yeah, oh yeah. I've been offered positions - I've been very blessed; I mean, I've been asked to give talks for different drug companies. But I've only given drug company talks for drugs I believe in. I don't talk for like sleep aids and stupid sleeping pills. I only work for certain companies. So, I'm very prideful about that. And so, I sought Harmony out and said, "Hey, look, dude. I really want to represent you guys…. I'm a very persuasive speaker. I'm passionate about what I do...I'm very enthusiastic, and I can talk to the wall; I can talk to anybody. So, I try to bring a lot of excitement to the drug talks…and the drug reps have told me, hey, we're getting people to write the drug for us…you put somebody with an MD in front of them, oh, I'll listen to that. But even still, there are other doctors that are complete douchebag idiots. They won't change anything about their prescribing habits because they think they know more than you and I combined. There's just, unfortunately, not a place for those. So, it's not really that people got excited. I got excited. But I'm a rarity, dude. That's the thing. It's very much a rarity…I think that I've played a big role—I think I've played a role personally with education in the country because I feel like I've really spoken to so many providers that they listen. I think they do”. - Physician and Harmony speaker in Alabama

Close relationship with his Harmony rep
Q: “Do you interact with the company? I always ask doctors what their impression is of the company, the sales rep?”
A: “My personal rep is a great guy. I actually am very fortunate to know his wife, who is a [redacted] in the community. He's a really great guy. He's Johnny on the spot, calls me back anytime I need something. I mean, the guy is just over-the-top great. I probably give lectures for probably five or six Wakix reps, and I do that regularly. So, I don't know what the turnover is. I'm not privy to that knowledge. But I can tell you that there are five or six reps that I've been giving lectures for, ever since 2020, like when the drug came out.” - Physician and Harmony speaker in Alabama

Source: Scorpion Capital consultation calls with experts
Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers

*Went nuts prescribing Wakix within “couple of days” of approval*
A: “I think it’s like November of ’19, it became available…and when that hit the door, I mean, as soon as I heard that it was approved, I called the rep and found out who it was. I wanted to know everything I could about it. I read everything I could, and then literally a couple of days later, we just started putting as many patients as we could on Wakix.”
Q: “And when was that?”
A: “This would be December of ’19, I believe…It was like literally right afterwards, and we probably went balls to the wall to get people on it because I have people that were not responding to other therapies…we probably got, like, in the first two months, we probably put 20 people on it. I mean, it was just sick because we saw all these narcoleptics.” - Physician and Harmony speaker in Alabama

*Every narcolepsy patient is offered Wakix*
Q: “How many total patients do you have? What’s the denominator for that 100 Wakix? Do you understand what I’m saying?”
A: “Absolutely. 100% of every narcolectic is offered Wakix. Absolutely. It’s a no-brainer. It’s not even scheduled. So, I mean, to not think of Wakix is not malpractice, but it’s absurd practice. So, we are extremely aggressive about offering Wakix…So, not everybody gets on it, but essentially, 100% are at least discussed.”
Q: “So, what is that denominator, roughly? What is your total addressable patient population on Wakix? It is 50%, 90%?”
A: “I would probably venture to say about 70% are on it, and some of that is because patients say they’re doing “so well” on their current regimen, and maybe they don’t necessarily want to change or increase, rather. But I would say a very reasonable number would be—maybe I shouldn’t say 70, I’ll say 60% because, like I said, we do recommend it for everyone, and 3 out of 5, if we write for it—I think your question is, are they on it? That was your question.”
Q: “Well, both. I know it’s hard to get approved. Do you typically just prescribe it 100%, and then the actual number ends up being a function of reimbursement and approvals and all that stuff?”
A: “We would write for, I would say, a solid 80% would be written for it, and then of those 80, I’d say about 80% get on it. Does that make sense? So, that comes out to about 65% of the patients that we see with narcolepsy get on the drug. It’s absolutely my go-to recommendation…” - Physician and Harmony speaker in Alabama

Source: Scorpion Capital consultation calls with experts
Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers

Doesn’t even think the drug is a game-changer; just a subtle effect and “adjunctive measure”

Q: “What do you hear from patients? Are they like, oh my god, two hours later, I feel amazing? What’s the distribution of patient feedback? What does that histogram look like?”
A: “No, it’s really not like that. It’s definitely not like a stimulant where you get this immediate effect. The way that most patients feel is that they notice some difference in terms of their daytime functionality, but they notice it more when they don’t take it. So, they oftentimes will not tell me, whoa, dude, you changed my life. It’s almost never that. It’s more of, you know what? I feel different. I feel like I can function better, and I’m thankful that you added this to my regiment because that’s how it is, we add it to regiments. We don’t take people off of things; we add it. It generally can take up to eight weeks to work…yeah, unfortunately, it doesn’t make people be like, oh my god, it’s a game changer. Most people don’t say that. But some do…I wish it was happening with everybody, but they need to be told, look, if it hasn’t happened yet, you got to stay on it. This is just our two-week or four-week follow-up, you gotta stay on it. And the majority of patients, I’d say 90% of the patients—it’s just speculation—but once we start it, they stay on it.”
Q: “You said for 90% of people, they don’t really feel a big effect, but if they go off it, then they realize they’re off it, so they want to stay on it, and then a small percentage, it’s like, wow, really noticeable.”
A: “So, the majority of patients do not come back and say holy hell, I can’t believe how awesome I feel. It doesn’t work that way. It’s an adjunctive measure to get people to feel improvement that they say, yeah, you know what? I do feel some improvement, and I notice it even more when I don’t take it. And that’s kind of the beauty of it.”

Saturated and harder to put more patients onto the drug

Q: “So, what do you think it’s going to be in a year? You think you’re going to have 200 patients on it? 150?
A: “That’s a very difficult question. We shot out of the box fast because all these narcoleptics that didn’t have it, we gave it to them and bang, our numbers went up like frickin’ hotcakes. I would think that we’re going to continue to put, I don’t know, probably one or two a month, maybe. Maybe one every month or so on it…but I don’t think that number is going to exponentially grow like it has.” - Physician and Harmony speaker in Alabama

Source: Scorpion Capital consultation calls with experts
Prescriber #8: Private practice doctor in Alabama who states he may be Harmony’s top prescriber in the US with 100 patients on Wakix, and that he’s one of their top speakers.

**Doesn’t run any tests or labwork, doesn’t seem concerned about side effects**

Q: "I was reading the label. They're not black box warnings, but they're kind of these moderately serious warnings about hepatic impairment, kidney impairment, QT elongation. Do those worry you? Do you have to run separate tests or panels, or you just think it's really safe, so you really don't have to monitor or test for that?"

A: "**I do not run any EKG’s.** When a patient says they've got things that are like palpitations or they feel dizzy, and by the way, that's never happened in my clinic, then we would tell the patient to stop, and we'd do a cardiology referral or ER or whatever. There are a lot of drugs out there that prolong QT. Some antibiotics, some antidepressants do. I mean, you don't run EKGs—most doctors that I'm aware of don't do EKGs before putting them on an antibiotic. So, I don't routinely do that. **I don't check lab work.**

**Remember, most narcoleptics that we see are pretty damned healthy people.** They may have a little bit of blood pressure; they may have a little bit of diabetes. People who have narcolepsy have a higher risk of these things. But they don't—they're overall healthy people...**No, I don't do lab work.**"

Q: "**And do you have a similar perspective on kidney and liver stuff** - that they're just young, healthy patients, so you think it's a waste of their time and your time?"

A: "Yeah, I mean, if they're presumed to be healthy, and there's nothing in their medical record to suggest otherwise, I **personally don't do additional lab work.** Now, there may be doctors that do—I can't vouch for how they practice. I have been doing it for a while but not as long as others. I've been around 15 years, but I just don't routinely do that." - Physician and Harmony speaker in Alabama

**Claims to not even know how much it costs**

Q: "How much is it? I know it's a pretty expensive drug. Do you know what the actual price is?"

A: "**No, I couldn’t tell you. I honestly couldn’t even guess**…we are very successful getting it approved. Now, I don't know what Joe Schmo, idiot doctor otherwise in Colorado, is doing, but we don't have much of a problem at all getting it approved."

Q: "My understanding is similar to the Jazz drug, I guess Xywav or Xyrem, I think it's like $120,000, $150,000 a year.

A: "What's $150,000 a year? I don't know what that means."

Q: "The price of the drug."

A: "**Holy shit. No... I have.. ho... I ... really? Dude, I swear to god I must live under a rock because I had no idea how much that goddamn thing is. That's stupid. But then the drug companies can write whatever they want, right? They can sell it for anything they want. That's unbelievable.**"

Q: "Yeah, it's super expensive.

A: "**That's unbe—wow. That’s sick. No, I didn't know that, and I don't even know how much Wakix is.**"

Q: "Yeah, I think it's about $120,000/$150,000 a year.

A: "**Wow.**" - Physician and Harmony speaker in Alabama

Source: Scorpion Capital consultation calls with experts
Prescriber #9: UK-based neurologist who has advised Harmony and until recently practiced in the US and used Wakix in both settings; long experience with the drug given involvement with the early access program. Now barely uses it with only 2 patients on drug; 80% discontinuation rate within 1-2 months; “failed drug” that never “really took off”; people “reluctant to use it”; last resort drug and “not aware of any high volume prescribers” – only dabblers, as institutions stopped using it; hasn’t come across a single doctor who raves about it. Lack of efficacy, drug-drug interactions, and side effects cause patients to discontinue. Drug-drug interactions are such a huge problem – “it interacts with everything” – that he advised Harmony they need a separate website to alert patients. Asked Harmony for data from the failed HARMONY 2 trial – which was swept under the rug – but was never given it.

**Started using Wakix years ago but has only two patients on it**
A: “My background is in neurology. I’m board certified in neurology and sleep medicine in the U.S. I’m kind of similarly board-certified in the UK and in Europe in sleep medicine now. So, I initially used Wakix in the U.S. for probably about two or three years before I moved back. And then, I’ve also had experience in using it in the UK. In the UK, I think I have about two patients on pitolisant currently for narcolepsy with cataplexy.”
Q: So, you have two patients on it in the UK, and what’s the denominator there?”
A: “The ones that I’ve seen and I know about are about 25.
Q: “So, you have less than 10% of people on it.”
A: “Yes.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings

**80% discontinuation rate within 1-2 months**
Q: “And what is your estimate of the discontinuation rate? If you have two patients, and how many in total have tried it at least once where they kind of got a prescription filled? What’s the denominator of those two that are on it?”
A: “I would say about 80% of the patients I’ve tried it on discontinued, within one to two months, most of them won’t stay on it. One, because of headaches, or they just don’t think it’s doing anything. And a lot of these people are working, so they can’t wait. You say give it three months to see the effect because it’s continued improvement, and they just say, "Well, I’m working. I can’t do this. I need something else now.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings
Prescriber #9: UK-based neurologist who has advised Harmony and until recently practiced in the US and used Wakix in both settings

Failed drug that never “really took off”; people “reluctant to use it”; “not aware of any high volume prescribers,’ only

A: “I don’t think pitolisant ever really took off, to be honest. People seemed to be a bit reluctant to use it for whatever reason. I think it may have to do with the titration schedule as well, that you have to titrate it over several weeks. And then the other thing, it’s all a little bit of a distant memory now, but the other thing was that it had to come from a specific pharmacy, I believe. But you had to fill out a form, and then their pharmacy would arrange for the drug to be sent. So, it was a bit of a hassle, I think that just generates people not using it… I don’t know of any high volume prescribers of pitolisant, to be honest.”

Q: “Do you know people that have stopped prescribing it completely or just don’t like it?

A: “I don’t really prescribe it anymore. My colleague at Columbia doesn’t think he uses it very often, either. And people at Duke I’ve spoken to, I don’t think they use it very often. I don’t think anyone prescribed it in high volume and then sort of tapered off. I think people dabbled in the water and saw no effect from it and just didn’t continue.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings

Last resort drug; docs don’t like it; haven’t found a single doc who raves about it

Q: “What do you hear from other doctors?

A: “Yeah, that it’s not very good [chuckles]. I think it’s interesting because, in the UK, they have even fewer drugs than they do in the U.S. And then I go, well, it’s not a great drug; it interacts with everything, and everyone gets headaches. And they say, yeah. But when you haven’t got many options, you go with the options you’ve got. It’s not a drug that I advocate. It’s kind of a last resort for me, and I don’t think anyone’s had—they’ve never been wowed by this drug, whereas Sunosi, solriamfetol, that’s a good drug. It’s surprisingly good.”

Q: “What do doctors in the UK and Europe say about it, like when you go to conferences or your peers?”

A: “They’re not all so wild about it as well because I remember before you go to moved back, I was talking to someone before I even knew about it, and they were saying, “Well, we have pitolisant.” And I said, “I’ve never heard of this.” And then, I think I spoke to them in Prague before they tried to launch it in the U.S. And they’re like, “Yeah, no one’s excited about it, and it’s not used very often because of the interactions or the effects.” So, it’s a similar thing. I haven’t found anyone who raves about pitolisant, to be honest.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings

Asked for Harmony 2 trial data and never got it – failed trial that was swept under the rug

A: “The first pivotal trial showed that it was inferior to modafinil, failed on EDS, I think. The second trial, I think, failed on pretty much everything, and they never published anything. This is Harmony 2, so they just kind of swept it under the rug. They never talked about it.”

A: “Yeah, I asked for that data, and they didn’t give it to me.”

Q: “You asked for the Harmony 2 trial data?”

A: “Yes, I asked them to send it to me. I don’t think I ever got it.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings
Prescriber #9: UK-based neurologist who has advised Harmony and until recently practiced in the US and used Wakix in both settings

**Lack of efficacy, drug-drug interactions, and major side effects that cause discontinuation**

Q: “I think, you had said that at one point, you had as many as 10, and now you have a lot less. Why is that?”
A: “People discontinue it for side effects or lack of efficacy or what is perceived as efficacy, I should say.”

Q: “Talk to me about both of those: discontinuation rates, lack of efficacy, and side effects. What have you observed? When do they happen? How significant are they, etc.?”
A: “In the U.S., I had early access to the drug before it was approved. So, we used it I quite a few patients then. The problem with the medication—it’s very interesting because it’s a new mechanism of action; there’s nothing like that. So, that’s quite exciting to think about from that approach. But it has drug-drug interactions, and that makes it much more complicated to use because a lot of these individuals have mental health issues as well, like anxiety/depression, so they’re on SSRIs, SNRIs, and they interact with the medication. So, that’s one problem. The other issue is that a lot of them are not naïve to the medication; they’ve tried other things, which, in my experience, if you add it in when people are on stimulants, a wake-promoting agent, they have headaches, and the headaches are quite significant that it makes them discontinue. So, that’s one thing. The other issue is it interacts with the birth control. Oral contraceptives. So, if they contain estrogen, that’s an issue as well; it interacts with that drug.”

Q: “So, you have issues if you take it with an SSRI? You have issues if you take it with a stimulant. You have issues if you take it with birth control.”
A: “[Chuckles] Basically, yeah.” — Neurologist in the UK who also practiced in the US; used Wakix in both settings

**Drug-drug interactions very prevalent — “it interacts with everything”**

Q: “Let’s walk through each of those different drug-drug interactions. If they’re on a stimulant and they take pitolisant, they get headaches that are bad enough where they discontinue?”
A: “Yes. That is my common experience of this. The headaches are the biggest limiting factor to this.”

Q: “And what percentage of patients are typically on stimulants? Most of them because they need to stay awake?”
A: “It wasn't first-line when I was there, so they had to have tried stimulants before they could get pitolisant.”

Q: “So, headaches with stimulants, and what happens with SSRIs? I think it increases the concentration of the drug.”
A: “It depends on which medication we’re talking about. Sometimes it increases it; sometimes, it decreases it because they work through different cytochrome P450 enzymes. But again, the most common side effect of all that will be a headache because it just drives monoamines. What they were doing when I left was that I advised the company that they should really have a website where you can—like drugs.com—where you can put in the drug that the patient may be on so that you can give advice about how it interacts rather than trying to figure it out yourself.”

Q: “So, you’re saying that the drug-drug interactions were so significant that you thought the company should have a separate website for people?”
A: “Yeah, absolutely. Because it interacts with everything.” — Neurologist in the UK who also practiced in the US; used Wakix in both settings

Source: Scorpion Capital consultation calls with experts
Prescriber #10: Neurologist in New York City at a leading medical center with 20 out of 100-120 narcolepsy patients on Wakix. Has now soured – “I was very excited initially based on the mechanism of action” – but has barely put any patient on in the last 6 months. “Pretty high” discontinuation rate – “a lot of patients just don’t want to stay on it.” Competes in “a pretty saturated field” of EDS and cataplexy drug and no better than “the current standard of care” with inexpensive generics like modafinil. Onerous to prescribe given reimbursement pressure and her “staff was spending a lot of time in that regard.”

Initially excited but now ambivalent; new starts have dropped in last 6 months; saturated field; reimbursement hassles; no better than standard of care with generics like modafinil

A: “I would say Wakix right now is probably about 20 patients. I was very excited initially based on the mechanism… but I have to say it’s a pretty saturated field, particularly if you’re just looking at narcolepsy with EDS or cataplexy. It’s one of many drugs that you can use. So, I’d say right now, it’s probably about 20 patients. I might have had a couple more patients on over the past six months or so.”

Q: “How many narcolepsy EDS patients do you have in total? What percentage of them do you have on Wakix?”
A: “I’d say probably about 100-120 patients with narcolepsy, EDS, and cataplexy. So maybe 10% or 15% on.”

Q: “When I was looking at the notes, it sounds like you used to have a lot more patients on, then you kind of soured on it or is this always the number you’ve had on?”
A: “I think it’s gone down a little bit. I think, especially upon launch or really within this first couple of months, I think there was a little bit more excitement, especially based on the mechanism…and then also, it’s a field where we have other therapies. We have therapies that we can use, first, second, and third-line. For EDS, they’re much easier to get covered. Cataplexy, we have oxybate, which I think works a little bit better. So, I would say, initially, I think based on the mechanism, the company support, and sort of this excitement on the whole histamine pathway…but I think in real-life clinical practice, it’s a little bit less right now.”

Q: “What did you begin observing that changed your mind? Was it discontinuation rates? Lack of efficacy? Side effects? All the above? Walk me through those observations that you had based on your clinical experience.
A: “Yeah, all of the above. I think, again, it was, well, number one, prescribing itself was just difficult in terms of access, essentially, really high out-of-pocket pocket cost, getting things approved, and some of my staff was spending a lot of time in that regard. And then I think, again, especially in like the EDS patients, where we really wanted to see this more in the way of wakefulness correlating with some of the ESS scores and so on. I don’t think it was better than the current standard of care that you could provide with Provigil and Nuvigil, a low dose of methylamphetamine, and things like that. So, I think, again, efficacy really wasn’t better than the current standard of care.” – Neurologist in the New York, major academic center
Prescriber #10: Neurologist in New York City at a leading medical center with 20 out of 100-120 narcolepsy patients on Wakix.

High discontinuation rate

Q: “Do you have a ballpark number in your head of what is the discontinuation rate that you've personally seen?”

A: “I want to say it's pretty high. It’s about 25% to 30%. Again, it's not a drug that works right away, so a lot of these patients they’re not de novo; they’ve been on drugs that work much more quickly, some of the SNRIs that we use, some of the amphetamines, things like that. You have to counsel patients. Maybe at two months, you might see a benefit, maybe three months. A lot of patients just don't want to stay on it. This is a younger population for the most part. They're busy; they don't want to try new things. So, it's about 25% that say, "It's not working. I felt better previously on something," or "I want to discontinue and try XYZ instead." – Neurologist in the New York, major academic center

Source: Scorpion Capital consultation calls with experts
Prescriber #11: Neurologist in Texas with “one of the largest narcolepsy patient populations in the US” 200 narcolepsy patients total, of which 50 are on Wakix. Has a long history with Harmony, serving as a key trial investigator, adviser, and speaker. One-third of patients discontinue – “most of the time, I don’t think it’s doing anything.” Complacent about the safety and doesn’t do cardiac screening – “I’ve only run an EKG on one such patient”; liver and kidney issues are “not monitored routinely in narcolepsy centers and sleep clinics as a major concern.” However, still exhibited some underlying concern: “I think that’s something that we’re going to have to watch with this medication.” Provided a narrative of a serious psychiatric adverse event in a patient with no existing history, which began 1-2 weeks after starting Wakix and stopped immediately when it was withdrawn – “she had uncontrollable bursts of anger, and she was like, slamming her desk and stomping her feet on the floor…that was a weird one…could have been…very profound…she doesn’t have any psychosis or bipolar or anything.”

50 Wakix patients out of 200 narcolepsy patients total
“My background is I'm board-certified in neurology and in sleep medicine. My practice is focused predominantly on sleep medicine, but you have the isolated neurology patient here or there, but more than 95% of the practice is sleep medicine. My background in sleep medicine is that—I don't know where it ranks—but I have one of the largest narcolepsy patient populations in the United States. By last count, I personally attend to over 200 patients with narcolepsy. My practice currently has three clinicians. It started with just me. Now we have two physicians and a nurse practitioner, and collectively, we manage a couple of thousand patients…I have somewhere between 50 and 75 patients on Wakix, let's say 50, to be safe.” – Neurologist in Texas, one of largest sleep practices in the US

1/3 discontinue due to lack of efficacy
Q: “So, about a quarter of them are on it. How many have ever tried it? How many discontinued to get to the 50? Just a rough guess.”
A: “Out of the people I try it on, maybe 1 in 3 of them stop it. Most of the time, it’s not side effects. Most of the time, I don’t think it’s doing anything…Some people have discontinued because of side effects.” - Neurologist in Texas, one of largest sleep practices in the US

Source: Scorpion Capital consultation calls with experts
Prescriber #11: Neurologist in Texas with “one of the largest narcolepsy patient populations in the US” 200 narcolepsy patients total, of which 50 are on Wakix. Has a long history with Harmony, serving as a key trial investigator, adviser, and speaker.

No cardiac screening; no cardiac risk; no hepatic risk; only run one EKG: complacent
“But with Wakix, it doesn’t really have any significant signal in terms of changing blood pressure or heart rate. I’ve been very comfortable adding it right on top. So, that’s actually been very useful as well… I’ve only run an EKG on one such patient because of that…the QT prolongation, I don’t think, is something that clinicians are particularly concerned about if they’re familiar with QT prolongation. As far as the other ones are concerned, you know, moderate hepatic impairment, renal impairment, the overwhelming majority of people that are getting diagnosed and treated for narcolepsy are teenagers and people in their 20s, or it goes a little bit later if they’ve gone longer with that diagnosis. Obviously, as time goes on, these people will get older…but the overwhelming majority of people I treat for narcolepsy are age 40 and under. And the reason why that’s relevant to your question is those people characteristically are much, much less likely to have issues with kidney and liver disease than people who are older. So, I think that’s why that’s not monitored routinely in narcolepsy centers and sleep clinics as a major concern. I do think that as time goes on and these people get older, I think that’s something that we’re going to have to watch with this medication.” – Neurologist in Texas, one of largest sleep practices in the US

Troubling psychiatric side effect in a patient with no existing history, started within 1-2 weeks
Q: “What’s the worst side effect you’ve ever had? Was it anxiety or something else?”
A: “No-no. The worst one I had was—and this is a weird one—a woman who went on Wakix, and when she was on Wakix, she had uncontrollable bursts of anger, and she was like, slamming her desk and stomping her feet on the floor, and angering her downstairs neighbors. She didn’t know why and she couldn’t control herself, and she realized it was the medication, and we stopped it. I, of course, reported that. I haven’t heard of that in anybody else, and I haven’t seen it. But that was a weird one. Again, not dangerous per se; I mean, I guess it could have been, but certainly very profound.”
Q: “How soon after starting the drug did that occur?”
A: “I think it was fairly early in the course. Within the first, either week one or week two.”
Q: “How quickly did it go away after stopping the drug?”
A: “I don’t think it lasted hours and hours, to be fair. But she realized that what was new was this drug, so she didn’t take it, and then she didn’t have it again. So, by the next day, for sure. But I don’t think it lasted hours and hours. I think it was an episode that occurred for a long enough period of time to be concerning, but then, once she stopped taking it, the next day.”
Q: “Did she have any psychiatric other stuff going on that made her more prone? Was it very surprising to her and to you?”
A: “It was surprising, yeah, I mean, because I think she has a history of depression, but that’s super common in narcolepsy, but there was nothing more than that. She doesn’t have any psychosis or bipolar or anything that would say we can just write this off as the fact that she’s had psychiatric illness.” – Neurologist in Texas, one of largest sleep practices in the US

Source: Scorpion Capital consultation calls with experts
Prescriber #12: Private practice physician in Northern California who is one of Harmony’s main speakers, with ~110 patients on Wakix out of 250 narcolepsy patients total, and stated he’s one of their top 5 prescribers nationally. Doesn’t even think the drug works and not enthusiastic: “...the main drawback is that it doesn’t work or works very little”; “not going to be like a miraculous wonder drug that goes nuts.” Wakix market opportunity is saturated and peaked a year ago; not much growth likely in new patients or new prescribers, even if they get other indications like idiopathic hypersomnia; got every prescriber they’re going to get. Estimates that top 5 Harmony prescribers nationally could be 5-700 patients – potentially ~30% of the company’s revenue, by our math. Complacent about safety and does no monitoring – “those items are just warnings...you don’t have to do anything.” Says Harmony won’t disclose the drug’s price to doctors and reps are allegedly instructed not to do so.

“...one of the more demanded speakers”
“Yeah-yeah, I've done a lot [of speaking events]. I max out every year with them quickly. I'm one of the more demanded speakers out there.” – Sleep physician in the Bay Area, CA

110 patients on Wakix out of 250 or so narcoleptics
A: “We have a large practice, thousands of patients, I see all the different types of sleep disorders, and I'm kind of a key opinion leader in terms of narcolepsy and narcolepsy treatments.”
Q: “Walk me through your history with Wakix. When did you first prescribe the drug? How many patients do you have on it now?
A: “We first started using they came out with their early access program when they were trying to get FDA approval. So, before it was FDA-approved, we had a chance to—we were the largest West coast site that saw these patients on pitolisant—and now, we probably have hundreds of patients on Wakix.”
Q: “If you had to estimate, roughly, how many do you think you have?
A: “Ballpark, probably like maybe 110.”
Q: “And what’s the denominator there? How many narcolepsy/EDS patients do you have in total?”
A: “I think probably in the practice in total, we have probably like 250 or so.” – Sleep physician in the Bay Area, CA

Source: Scorpion Capital consultation calls with experts
Prescriber #12: Private practice physician in Northern California who is one of Harmony’s main speakers, with ~110 patients on Wakix out of 250 narcolepsy patients total, and stated he’s one of their top 5 prescribers nationally.

**Not first line, only second or third line**
A: “It’s best to use, in my opinion, adjunctively with other medicines.”
Q: “So, you’re not really using it as a first-line treatment—it’s typically part of a cocktail, like a second, third, fourth-line treatment? Is that correct?”
A: “…we have a lot of patients that are taking it as a second or third medication.” – Sleep physician in the Bay Area, CA

**Doesn’t even think it works**
“The main drawback of this is that it doesn’t work or it works very little.” – Sleep physician in the Bay Area, CA

**Not enthusiastic**
“I think overall, it’s not going to be like a miraculous wonder drug that goes nuts. It’s going to be a medication for those that are really, truly interested in treating narcolepsy or hypersomnia and have that interest and willing to be a little more patient with not only their patient population but other medications.” – Sleep physician in the Bay Area, CA

**Estimates that top prescribers could be 5-700 patients total**
Q: “Are you their largest prescriber in the country? How many other guys are there that are prescribing with more than 100 patients on it?”
A: “A lot. At one point, they did tell me I was top—but I think I’m top five now because there are a couple of others on the East coast that have taken over.”
Q: “How many patients does their biggest prescriber have?”
A: “I don’t know. Honestly, I have no idea of that number. But my guess is probably, I’m sure there are some East coasters in probably the 200-plus range, or 150-plus range or something like that is my guess.”
Q: “So, like the top 5, could be what? Like 700, 1000 patients, something like that?”
A: “You mean, how many total would that be? Yeah. I would say, yeah, probably that range, right, like 500 to 700 patients, something like that, yeah.” – Sleep physician in the Bay Area, CA

Source: Scorpion Capital consultation calls with experts
Prescriber #12: Private practice physician in Northern California who is one of Harmony’s main speakers, with ~110 patients on Wakix out of 250 narcolepsy patients total, and stated he’s one of their top 5 prescribers nationally.

_Saturated and peaked a year ago; not much growth likely in new patients or new doctors who prescribe it, even if they get other indications; got every prescriber they’re going to get_

Q: “When was the peak enthusiasm? Or is this still growing and getting better? Or did it peak and not it's kind of more tapered off?”
A: “Enthusiasm from the medical community, you mean?...It did peak maybe like a year ago or so, but now I think it’s tapered off a little bit. I think the biggest hurdle has been the whole insurance process of getting it, which is, a lot of the time, the hurdle for a lot of these practices. They don't want to do the extra work that's required to get the medication for their patients. I think that's a hurdle that limits enthusiasm.”

Q: “And so, you have 110 on it now. How many do you think you're going to have on it next year? Do you think it's going to be steady at like 110, more or less, or is it going to go to like 150-200 over the next year or two?
A: “No, I don’t think it's going to go up that much. Once they get the idiopathic hypersomnia, I might be able to use it more, but honestly, it'll probably go up to like 120-130, something like that.”

Q: “So, like another 10% to 15%, maybe?”
A: “Yeah. We had a large number of people started on in the trial. So, in terms of finding new patients and getting them either newly diagnosed or getting them switched over the therapy, I don't think it's going to ramp up by crazy amounts.”

Q: “Are there more high-volume prescribers that you think they're going to get? Or did they get them all right away? Could their growth be that they don't have a lot—they already got all the other doctors like you, the large sleep practices or are they still getting more of them? You can see what I'm trying to figure out. I'm just trying to figure out how saturated their growth could be. So, either you get more doctors or you get more patients per doctor. It sounds like there's only so much room in terms of patients per doctor. So, I can't imagine there are that many narcolepsy specialists out there.”
A: “They're not, and, in my opinion, when a medicine like this first comes out, all the narcolepsy specialists gravitate to it. We like to try things. I think they probably have gotten the large majority of narcolepsy specialists out there, and I don't see them all of a sudden running into huge practices and taking over for—I don't see that happening. I have a feeling it's kind of saturated from that angle...I think most of the prescribers that are going to get on board are going to be these types of prescribers that are like onesies, twosies, threes—they're not going to be high-volume ones.” – Sleep physician in the Bay Area, CA
Prescriber #12: Private practice physician in Northern California who is one of Harmony’s main speakers, with ~110 patients on Wakix out of 250 narcolepsy patients total, and stated he’s one of their top 5 prescribers nationally.

**Complacent about safety issues and appears to do no patient monitoring**
Q: “I looked at the label, and there were some relatively serious things like moderate hepatic impairment, QT prolongation, renal issues, and drug-drug interactions. Do doctors even have time to monitor for that stuff? What are you observing as far as how people handle those items on the label?”
A: “Those items are just warnings. You’re not going to run into those issues hardly ever. I mean, to date, I’ve never ordered an EKG on a patient. That’s what I tell doctors; these are just warnings. I think the biggest thing is a doctor is going to know if a patient has severe hepatic impairment or not. That’s just obvious. And then, if someone has QT interval prolongation, you’re going to be followed by a cardiologist. But you don’t run into those issues. There are so many medicines already out there that cause QT prolongation that don’t even have it on their label, and this is just this company being very conservative. Will it impact prescribing? To some degree, yes—some doctors may be more hesitant to prescribe it or want to take all the precautions before they do anything, **but technically speaking, you don’t have to do anything. You can just prescribe it, which is what we do.**”
-Sleep physician in the Bay Area, CA

**Harmony allegedly won’t tell doctors the price; reps say they’re told not to disclose it**
Q: “How much does it cost? It’s like $100,000-200,000 like that for the drug or something? Do you know what the price is?”
A: “**We’ve never been told the price.** I mean, we’ve always been told it’s cheaper than Xywav. Xywav costs a lot. But my guess is it’s in the 10-15 grand a month sort of price range.”
Q: “Have you asked about the price, and they won’t tell you? That feels a bit unusual that they don’t even tell the doctor the price?”
A: “**Oh, we’ve asked, and they don’t tell us** because we ask the reps, or maybe they’re higher-ups, and they say the same thing. We don’t know. Unless you get to, like, I guess, the top, I have no idea how to get that information.”
Q: “How is that even possible that a company sells a product and claims it doesn’t know the price and doesn’t want to tell doctors the price?
A: “Well, the reps and all of them, they’re the ones that are saying this, right? Because **they’re saying that’s what they’re told, and they’re told to say** basically that, hey, listen, don’t worry, the cost is going to be covered, meaning that they’re not going to bill the patient out of pocket, which is very true. …so, from that angle, what their point is, don’t worry about the cost; we’re going to make sure your patient gets it. But, so… right. So, it is expensive.”
-Sleep physician in the Bay Area, CA

**“Reimbursement hassle” is enough to make doctors “give up”**
“The **biggest reimbursement hassle** is you have to fail other medicines, usually the failure of modafinil and/or stimulants. Generally speaking, you've got to prior authorization, and you've got to fail other medicines, and I think doctors, generally speaking, especially if they're not so interested or focused on narcolepsy, **kind of give up.**”
-Sleep physician in the Bay Area, CA

Source: Scorpion Capital consultation calls with experts
Prescriber #13: Neurologist in Los Angeles-area who sees 20-50 narcolepsy patients per year. Initially excited to try Wakix and prescribed it to 20 patients but now has zero: “recently I’ve stopped prescribing it because it doesn’t really do anything.” His usage peaked in 2021 – “…and I think I’ve given it a fairly good try…it was very disappointing.” Experienced a 100% patient discontinuation rate and didn’t help a single patient: “nobody wanted to continue…what’s the point, right?”

Large practice with 20-50 narcolepsy patients per year
“I'm a neurologist. I'm in a suburban community. I see about maybe 500 patients per month. In terms of narcolepsy patients, I see anywhere between 20 and 50 per year.” -Neurologist in greater Los Angeles area

Tried it on 20 patients – “given it a fairly good try” - but doesn’t work; 100% discontinuation rate
A: “I tried it out early on when it first came out. And after trying it on a number of patients, like 20, it doesn't really work as well as Xyrem or Xywav, the other medications that came out much earlier. My patients have given me honest feedback. They haven't really seen much improvement. Recently, I've stopped prescribing it because it doesn't really do anything.”
Q: “And how long did it take you to get up to 20 patients? Is 20 the cumulative total you prescribed to, or did you quickly get up to 20 and then you started tapering off?”
A: “Not that quickly. I think maybe it took about six months because you have a lot of stable patients, and some patients sometimes they want to try something different or they want to add it on to their Xyrem and see if it works better.”
Q: “And so, when did your usage start to drop off? When did you peak, and when was--?”
A: “I think the peak was probably maybe about last year, towards the end of this time of the year, it peaked, and then starting around summertime of this year, I'm like, this is not working. It really hasn't. And I think I've given it a fairly good try. Patients have been on it for a couple of months, and it really didn't do anything. It was very disappointing.”
Q: “What would happen? Patients would come back to you, and they would say, "Dr. Back, this isn't doing anything for me?"”
A: “Yeah.
Q: “And so, how many do you have on it now?”
A: “None—nobody's on it because it didn't do anything, yeah.”
Q: “So, you have 100% discontinuation?”
A: “Nobody wanted to continue. Yeah. They didn't want to continue. What's the point, right? Wakix is not the only medication where it's kind of been a little lackluster. And then when you tell the company, of course, that's not what they want to hear. They want you to continue to prescribe, but I'm going like, I don't see much point in prescribing after prescribing like 20 patients; you don't really get anything? Then why would I... there really is not even, like, there wasn't like one dramatic patient. It really didn't do anything. It just didn't do much of anything.” -Sleep physician in great Los Angeles area
Prescriber #14: Neurologist and professor at a pre-eminent medical school, medical advisor to Harmony with a long relationship with the company. Large narcolepsy practice with >100 patients but hasn’t used Wakix in more than ~10 patients cumulatively: no better then generics like modafinil; “doesn’t really knock it out of the park”; “can’t think of a single patient where we’ve used Wakix as monotherapy.” Laughed and said he couldn’t say Wakix is any better than a placebo, and thinks competing drugs like oxybate class are stronger.

Large practice with >100 narcolepsy patients
“I’m a neurologist at a big Boston academic hospital. I only see sleep disorder patients, and my clinic is very skewed towards narcolepsy. I take care of more than 100 patients with narcolepsy. I also spend a lot of my time doing research on the basic mechanism through which drugs work in narcolepsy.” -Neurologist and professor at a pre-eminent academic institution

No better than generics like modafinil and worse than oxybates, so haven’t used it in more than 10 patients; only a combo therapy
“I think pitolisant is a useful tool in our choice of medications that we use for treating narcolepsy. To really get to the bottom line, for what it delivers, I find it sort of annoyingly expensive. As a comparator, sodium oxybate and the low-sodium oxybate are also even more expensive, $150,000-plus per year. But they also can produce pretty high efficacy. Pitolisant is a well-tolerated drug, but its efficacy in my mind as far as treating sleepiness is not all that different than, say, modafinil. To be honest, I haven’t actually used it in more than maybe 10 patients at this point. But my impression with most of them is that, yeah, it’s helpful, but it doesn’t really knock it out of the park. And so, I would say that’s actually the biggest reason why I haven't prescribed it more is just because people say, yeah, it's okay, but they usually need something else on top of it…I can't think of a single patient where we've used Wakix as monotherapy. It's almost always in combination with other meds.” - -Neurologist and professor at a pre-eminent academic institution, advisor to Harmony

Not even sure it’s better than placebo; sodium oxybate is better
“Well, I think it was a little better [ESS score] reduction than that. But I’d have to go back. I haven't actually looked at those original papers for a couple of years now…well, I remember it was not much. My clinical impression is that when it comes to efficacy, oxybates are stronger, and the oxybate trials generally showed a better separation from placebo in this regard. The higher dose was like 9 grams of oxybate per night, separate really well from placebo, and pitolisant didn't, and that’s why… I do think it's... [chuckles]... I would like to think it's better than placebo, but I'd have to say I can't say that numerically I have much data to support that beyond what's in published papers.” - -Neurologist and professor at a pre-eminent academic institution, advisor to Harmony

Source: Scorpion Capital consultation calls with experts
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. We note the patient did not meet any of the QT-related precautions on the label. He disclosed the risk to his patients - and all but two quickly discontinued.

Large practice with 50 narcolepsy patients; was keen to try it after reading the literature and doing research
“I've got about, at this point, narcolepsy patients past and present are getting up to about—it came closer to 50-something patients. And the big issue, obviously, is the excessive daytime sleepiness in patients where it's interfering with normal activities and work, things like that. So, of course, Wakix was something that sounded very interesting because the consensus was that this wasn't something that would be addictive or patients wouldn't become dependent on it. And so, you read the studies, you talk to the reps, and everybody’s pretty excited about it. Based off of literature, it sounded like it was the next thing in terms of treating this. So, obviously, it was something I came across in literature, and at a meeting, I decided to give it a try. For the most part, I didn't really have any major issues, but when you get patients who have significant cardiac arrhythmia that they could potentially die from and it kind of causes you to maybe pause a little bit and say, hey, maybe more data needs to be collected, and maybe we shouldn't be first in line to jump on the bandwagon and kind of see how things play out. And that was my response to having patients who had experienced long QT syndrome.” -Neurologist at a large hospital system in a Midwest state

Only two of ten patients left on it due to QT issue with one patient, who was “a clean, healthy patient, no history of any cardiac issues or arrhythmia”
Q: “When did you first prescribe it?
A: “Last year.
Q: “How many patients did you prescribe it to in total since then?
A: “About 10.”
Q: “And how many are still on it?
A: “Two are still on it. The other 8, after having a discussion with them about the cardiac issue, they opted to stop taking it.”
Q: “So, you had a conversation with the patients about the QT prolongation issue, and they decided to not take it anymore?”
A: “That’s right. And this was, obviously, it was presented initially because it's on the label. It was like, well, you know, there's a small chance this could potentially happen. As with anything, we kind of looked at it as a very, very small chance, but I always tell the same patients as well that even if the risk of something is 0.01% when it happens to you, it's 100%. So, your perspective on it kind of differs. Obviously, having a patient in the practice, you have that—even though we’re not certain, you know, like, yeah, we don't know 100%, but this is a clean, healthy patient, no history of any cardiac issues or arrhythmia.” -Neurologist at a large hospital system in a Midwest state
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. He disclosed the risk to his patients - and all but two quickly discontinued.

Otherwise healthy 42-year old taken to emergency room within two months of starting Wakix and diagnosed with QT prolongation

Q: “So, what happened with the patient with the QT prolongation?”
A: “Like I said, a pretty healthy guy otherwise. He was at dinner with his wife, and all of a sudden, he got diaphoretic, sweaty. Kind of said, I’m not feeling very good, clammy and diaphoretic. His wife happened to be a nurse. And she said, if you don’t feel well, let’s go home. So, on their way home, he was really just somnolent, not feeling good. They get home, and she happens to have a BP machine at home that also checks heart rate and sats. She checks it and his heart rate is just off, and she’s checking his pulse, and it’s irregular. And so, she’s worried that he’s having a heart attack. Obviously, she calls 911. They take him into the hospital, hook him up, and it’s clear as day that he’s got an arrhythmia, and initially, they thought maybe he was a-fib because his dad had a history of a-fib but upon further review by cardiology and electrophysiologist saw him, and they’re like, oh yeah, he’s got a long QT. And so, with the family history of a-fib, they’re like, well, this is not a-fib. And they were going through all the medicines like that, anything new, medical history. They kind of said, hey, this is a newer medicine that you said. The cardiologist was pretty astute. He kind of looked up the info and said, hey, this medication can actually cause that, and I don’t know necessarily that that’s what caused it, but certainly something to talk to your neurologist about. So, they work him up. He gets discharged and follows up with me. He’s like, hey doc, this is what happened. And then I’m like, whoa, okay. In that case, the first thing is we’re going to stop that medicine and see how things play out. So, obviously, we did.”

Q: “And how long had the patient been on Wakix before this event occurred?”
A: “He had been on it for 8 weeks, 2 months.”

Q: “And what was the age of the patient?”
A: “Forty-two. So, needless to say, it caused everybody to pay a little bit more attention.”

Q: “At 42, was the person obese or had other cardiac morbidities? You said the person was otherwise healthy or pretty healthy?”
A: “Yeah, pretty healthy guy. There is, overall, no real medical history. You know, blood pressure’s up a little bit, but nothing major. He was taking one antihypertensive, and he was well-controlled on that.”

Q: “So, the patient is only taking one antihypertensive for mild elevated blood pressure, 42, healthy, shows up in the ER with QT prolongation.”
A: “That’s right..” -Neurologist at a large hospital system in a Midwest state
Prescriber #15: Physician at a large hospital system in the Midwest with 50 narcolepsy patients, who as initially keen to try Wakix after studying the literature and put about a dozen patients on it. Became alarmed after a 42-year old patient was hospitalized for QT prolongation. He disclosed the risk to his patients - and all but two quickly discontinued.

No red flags in the patient; two days in the hospital; presented at the ER diaphoretic, somnolent - “going to pass out”

Q: “There are all of these CYP2D6 issues where depending on your genetics, your phenotype, you can have – and what was the ethnicity of the patient?”
A: “He’s a Caucasian patient. To our knowledge, no cytochrome people should use metabolic mitochondrial –”
Q: “And it sounds like you're a diligent doctor. Did you do a full panel before the drug to check for renal/hepatic impairment, metabolism issues, and all that stuff?”
A: “Right, absolutely. Absolutely. Nothing, no red flags or anything.”
Q: “And so, the patient who had these symptoms went home, and then what happened? What was the chronology? They just didn’t take anything at home? How long did it take for the symptoms to resolve?”
A: “So, the symptoms did resolve. I can't remember what medicine they got in the hospital. They got something, some kind of antiarrhythmic in the hospital, IV for the two days they were in the hospital, and everything kind of normalized. The patient went home and followed up with a cardiologist.”
Q: “The patient was in the hospital for two days?”
A: “Two days. Obviously, the cardiologists were working this up. They want to blue light everything, so stress test, echo, everything. That ended up being a two-day issue.”
Q: “What did the ER or the cardiologist see that put the patient in the hospital for two days?”
A: “When the patient was still symptomatic, so the patient was still diaphoretic, not feeling good —in addition to checking cardiac enzymes, the patient was hooked up to a - the patient was diaphoretic, felt like he was somnolent, going to pass out—things like that. So, obviously, when they saw the patient in the ER, they had to work it up.”
Q: “So, the patient’s diaphoretic. I had to look that up. That's excessive sweating.”
A: “Feeling somnolent and lethargic and tired--
Q: “That they could pass out?”
A: “Yeah, when the patient showed up in the emergency room, they checked cardiac enzymes. They had to rule out myocardial infarction. So, EKG, cardiac enzymes. The patient’s long QT just didn’t refer immediately, so the patient was admitted into observation, hooked up to a monitor, so for telemetry monitoring for heart rate and rhythm strip for 24 hours. The cardiologist wanted to get an echocardiogram to make sure the ejection fraction was standard. Basically, what they were trying to rule out was an underlying cardiac issue.” -Neurologist at a large hospital system in a Midwest state
Doc told the Harmony rep; rep was concerned it was a healthy patient – not one who met the cardiovascular/QT prolongation warning on the label
Q: “Did you talk to the company or sales rep about it?
A: “I did mention it to the sales rep.”
Q: “What did they say?
A: “The sales rep was also kind of a little bit concerned and said, geez, we know it can do this, but one of the things he said was, not in very healthy people, it’s usually people who have some other issues going on, but we know it can cause this. So, that was kind of it, and he just kind of said, well, obviously, even if we don’t know for sure, that this is what caused it, and I’m hoping the patient is off of the medicine.”. -Neurologist at a large hospital system in a Midwest state
Prescriber #16: Neurologist and sleep specialist in Chicago, a speaker for Harmony, who has 30-40 patients on Wakix out of 100-300 narcoleptics. Only uses it because “it’s better than nothing” and is “absolutely not” a “wonder drug.” Exclusively uses it as a combo therapy and “adjunct backup.” Has no idea how much the drug costs.

30-40 patients on Wakix out of 100-300 narcoleptics
A: “I'm in Chicago. I am a small private practice, neurology background, but I primarily just practice sleep. I've been practicing only sleep for most of my career. And narcolepsy patients, gosh anywhere from 100 to—we have quite a large base. It's hard because, in any given week, I can see 30 or zero. So, I'll say 100 to 300, maybe.”

Q: “When did you first start prescribing Wakix, and how many patients do you have on it?”
A: “We started prescribing as soon as it was available on the market. I'll say 30 or 40.” - Neurologist and sleep specialist in Chicago, speaker for Harmony

Only uses it because “it’s better than nothing”; “absolutely not” a “wonder drug”
“So, one of the reasons I'm so positive about any medication that's coming to the market, regardless of whatever downsides there may or may not be or whatever limited potential there may or may not be, it's better than nothing. Is it the wonder drug? Absolutely not.” - Neurologist and sleep specialist in Chicago, speaker for Harmony

Exclusively a combo therapy – “adjunct medication”
A: “I usually use this as an adjunct medication. For me, it's just the conceptualization of narcolepsy and how these medications work. And so, the way that I use it sort of to boost the potential of what you're already using. Again, a loose analogy is kind of like you can take the pill for birth control, or you can use condoms as birth control. You can take the pill for birth control, but it doesn't prevent sexually transmitted diseases, and in those cases, you take the pill and use the condom… So, a lot of times when I use Wakix, I use it as sort of an adjunct backup.”

Q: “What percentage of your Wakix patients is it combo therapy?”
A: “Almost all of them.” - Neurologist and sleep specialist in Chicago, speaker for Harmony

Has no idea how much the drug costs
A: “Reimbursement for Wakix. I had no idea. I don't get paid for the Wakix. I have no idea what the reimbursement is.”

Q: “Do you know how much the drug costs?”
A: “I have no idea. The only time we deal with the cost of medications is, I know that when I have a patient who doesn't qualify, like on Medicare, it's several hundred dollars per month, and that is frustrating because the big sell of the medication is—”

Q: “The drug is $180,000 a year.”
A: “Oh wow, yeah. That's expensive.” - Neurologist and sleep specialist in Chicago, speaker for Harmony

Source: Scorpion Capital consultation calls with experts
>Wakix’s only selling point – that it’s not a controlled substance – was dismissed by physicians as irrelevant
Harmony’s sales and marketing for Wakix has one and only angle – that it is easier to prescribe because it’s not a controlled substance. Given that Wakix is inferior to cheap generics like modafinil and physicians at best use it as a third or fourth line drug in cocktail, it has no other reason to exist. The DEA has classifies drugs from schedule 1 to 5, which creates certain requirements: 1) physicians have to be registered with the DEA in order to prescribe them; and 2) they can only write a scrip for 1-6 months of the drug, depending on its schedule level, which means their offices have to write scrips at regular intervals. Modafinil is schedule 4, which means a physician can write for a 6 month supply – making Wakix’s value proposition dubious. However, amphetamine-based stimulants for narcolepsy, like Adderall and Ritalin, are schedule 2, and doctors can only prescribe a 90-day supply at a time.

Wakix.com patient and physician site push the non-controlled angle; table of schedules per Wikipedia

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<th>Schedule</th>
<th>Potential for Abuse</th>
<th>Accepted Medical Use?</th>
<th>Potential for Addiction</th>
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<td>None</td>
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</table>

Source: https://en.wikipedia.org/wiki/Controlled_Substances_Act
Unfortunately for Harmony, every single physician we interviewed indicated there is no value proposition to Wakix being non-controlled: 1) prescribers are already registered to write controlled substances; 2) they have to write periodic refills for Wakix patients anyway as it’s a third or fourth line drug that is almost never used as a monotherapy, and the other drugs in the cocktail are controlled substances; and 3) Wakix’s centralized pharmacy is far more onerous to deal with than controlled drugs. We quote numerous doctors on the following pages who repeat the same refrain. One KOL said he sees “absolutely no benefit from it”; that “it doesn’t matter”; and that “I don’t know what the big deal is.” A Southern California specialist stated “what kind of value is there? I don’t see it.”

“Absolutely no benefit from it”; “it doesn’t matter”

Q: “One of the supposed advantages of Wakix is it’s not a scheduled or controlled substance, like some of these other medications. Is there any big advantage from it not being a controlled substance?”
A: “You know, sometimes, patients bring it up, but I don’t think there’s any big deal because, for me, I’ve still got to prescribe medicine, so I see absolutely no benefit from it.”

Q: “Yeah, it seems like the doctors are all already registered.
A: “Yeah, you have to prescribe something anyway; it’s just a couple of clicks. So, I don’t know what the big deal is...so, Wakix is less scheduled, but it doesn’t matter.” – Neurologist who is a sleep specialist and professor at a leading institution

“I don’t see” any value from it

Q: “The company says this is not a scheduled drug. Is that really an advantage?”
A: “I prescribe a lot of scheduled—like whether it’s Adderall or modafinil or like all of these. It’s a little bit of a hassle because you do have to plug in an extra code when you write these controlled substances, but at the same time, as a doctor, you want to give a medication that works because then, I mean, first of all, it’s about the patient. You want to improve their health. You want to improve their condition. And second of all, if you’re a doctor prescribing medications that don’t even work, I mean, what type of value is there? What kind of value is there? I don’t see it.” -Sleep physician in great Los Angeles area

Source: Scorpion Capital consultation calls with experts
A physician who is a medical advisor to Harmony concurred, saying “it’s not that big a deal” as scheduled drugs can still be prescribed for 6 months at a time, particularly key competitors like Xywav and Xyrem, and that the additional work is “not much.” He stated he already has to write scheduled drugs for all the same patients anyway: “most patients I treat with narcolepsy are going to be a 2 or 3-agent regimen, and those are going to involve things that are at least Schedule 4.” He added that “the folks at Harmony market that stronger than probably it carries with clinicians” and indicated it’s at best an incremental benefit.

“It’s not that big a deal”; Scheduled substances can still be prescribed for up to 6 months at a time

Q: “When something is Schedule 3 or Schedule 4, like Xyrem or modafinil, what is the requirement? How often does the patient—what is onerous about it being Schedule 3 or Schedule 4? What requirements does that involve?”

A: “Not much. Schedule 3 and Schedule 4 can both be written with refills going as much as 6 months. My Xywav prescriptions, I have to refill twice a year, the same thing with modafinil. So, it’s not nearly as onerous as Adderall, where you have to write a new script every month…Schedule 2s are more annoying. Three and 4 are the same, honestly. It's not that big a deal.”

Q: “And most of the drugs in this category are Schedule 3 and 4? The common ones?

A: “All of the stimulants are Schedule 2. So, Schedule 3 is just Xyrem and Xywav, and Schedule 4 is modafinil, armodafinil, and Sunosi. All of the stimulants: Adderall, Vyvanse, and Ritalin, are all Schedule 2.” – Medical advisor to Harmony

Incremental benefit at best; docs have to prescribe scheduled substances anyway

Q: “How much of an advantage is that Wakix is not controlled – aren’t all the people prescribing this already registered with the DEA?”

A: “It depends. Your point is well taken. For instance, from my perspective, most patients I treat with narcolepsy are going to be a 2 or 3-agent regimen, and those are going to involve things that are at least Schedule 4, sometimes Schedule 2, and Xyrem in between Schedule 3…there are other clinics that are very, very happy to just keep writing stimulants for everybody, and they don't want to deal with this, but at the same time, those are the people who are the most resistant, I think, oxybate, and the fact that this is a simple regimen, that also is a factor. I think the major challenge for any of the newer agents, there's a lot of inertia for some of these clinics where stimulants get approved, they’re cheap, you write it, the patient goes and picks it up at the pharmacy, that's it. There's no prior auth, there's no appeal, there's no annoying paperwork. And that happens with oxybate and with pitolisant. So, some people, whatever they say, they just don't want to deal with it. But that was a tangential answer, I'm sorry. But I do think it has some benefit to having it not being controlled. I think that the folks at Harmony market that stronger than probably it carries with clinicians, but it's not nothing.”

Q: “No, I get it. It's an incremental benefit.”

A: “Yeah.” – Medical advisor to Harmony

Source: Scorpion Capital consultation calls with experts
Every physician we spoke to slammed how onerous and unusual Wakix’s centralized pharmacy is, stating that it’s actually more difficult to use than controlled drugs, thus negating any potential benefit. We suspect Wakix runs it this way as part of its off-label scheme, which we detail in another section, which requires centralized control over its hub and specialty pharmacies. We quote two different prescribers below. One stated “they made it so difficult...because of the centralized pharmacy...any benefit...is basically in the wash...practically meaningless.” A second said “they play the schedule thing really high” but detailed “what you have to jump through” with Harmony instead – “it shouldn’t be this hard.”

“Meaningless” benefit from non-controlled substance given Harmony’s centralized pharmacy “made it so difficult”
Q: “How big a deal is the fact that it’s not a controlled substance?”
A: “If you would have talked to me before I started prescribing it, I liked that part of it. If I’m prescribing to you, if it’s an elevated Schedule, that means that I have to write out a new script every single month. Every single month, you and I, for as long as I’m taking care of you, I’m writing down something for you every single month for the rest of your life and the rest of my clinical practice, and that’s a pain in the ass, which is, that’s fine, that’s the deal when you’re dealing with a controlled substance. I get it. I was quite excited about that. But then they made it so difficult to get because of the centralized pharmacy, because of the cost and the prior authorization. Any benefit you would get from that is basically in the wash. That’s practically meaningless.” - Physician and professor of neurology at a large academic center; 120 narcolepsy patients

Harmony overplays the benefit: “they play the schedule thing really hard”; Harmony is harder to prescribe
Q: “Is there any benefit to this being not scheduled?”
A: “It’s all about the pre-authorization and what you have to jump through independently. Even if you’re on a drug that’s a controlled substance, you’re picking the right patient for it...they play the schedule thing really high, but it’s more about how much work you have to do to get that person on the drug, and now you have to fill out a form, you need to get a pre-authorization, you need to possibly not be on another drug. It’s a little tough. That’s just my opinion. I feel like it shouldn’t be this hard.” - Physician in private and academic practice in PA with 30-40 narcolepsy patients

Source: Scorpion Capital consultation calls with experts
Three additional physicians quoted below echoed the color: that they “hate” having to deal with Harmony's pharmacy; that they’re “quite disappointed” at the “burden of prescribing” Wakix; and that even though “they drove that home” as the selling point “but they just make it so complicated when they had their own pharmacy delivering it. Again, yeah, I think it hasn't taken off.”

**Doctors “hate” having to deal with Wakix's pharmacy**

Q: “How difficult was it for you to prescribe Wakix? Because you've got to call their hub and send in forms.”
A: “It's so infrequent, it's definitely a hassle, but it's so infrequent that it's okay. Like I said, I haven't done it for, my gosh, months and months right now.”
Q: “And what is it that makes it a hassle?”
A: “Oh, I just hate any—you know, I just like to go to my little prescription box, type it in, and submit. I hate having to fill out a separate form and all this other crap. You always have to, like with Wakix.” – Neurologist who is a sleep specialist and professor at leading institution

**Docs “quite disappointed” at the “burden of prescribing” Wakix**

A: “I think the excitement for this is on the wane.”
Q: “What are you observing there, aside from your own experience? What are you observing that leads you to think that?”
A: “The peak excitement was right before we started prescribing it, and then realized that there was going to be a centralized pharmacy, and the fact that they were pricing it so high was going to take all the convenience away of the lower FDA Schedule…the question you asked me was, what is the impression on behalf of sleep specialists? This was something that we were fairly eager and excited about, and then quite disappointed by how the burden of prescribing has really interfered with our ability to get people on it.” – Physician and professor of neurology at a large academic center; 120 narcolepsy patients

**Harmony “drove that home” re being non-scheduled, but Wakix is “so complicated” given centralized pharmacy**

“I mean, the one thing that was going for it was it was non-scheduled. They drove that home, that it's non-scheduled, and I think it was more of a mindset that it was a safe medication so therefore it didn’t have to be scheduled. But they just make it so complicated when they had their own pharmacy delivering it. Again, yeah, I think it hasn't taken off.” – Neurologist in the UK who also practiced in the US; used Wakix in both settings

Source: Scorpion Capital consultation calls with experts
Mechanism of action – “increases histamine levels in the human brain” – is unproven and hence false advertising
Harmony markets Wakix to patients and doctors as a “first-of-its-kind medication that increases histamine levels in the human brain” – the critical claim upon which the entire premise and purported mechanism of action rests. However, neither Harmony nor Bioprojet has ever shown this to be the case, which means there is no evidence for the key claim and that their advertising and marketing is therefore false, in our opinion. The patient-facing website prominently features the very specific claim throughout, including right at the top of the home page.

Wakix.com screenshot

Source: https://www.wakix.com/
The “How Does WAKIX Work” page prominently features a video that graphically shows histamine being increased in the human brain. The “Mechanism Of Action” section on the site for healthcare professionals pushes this claim just as loudly.

Patient site (www.wakix.com) at top, and healthcare professionals site below (www.wakixhcp.com)
Harmony shows no citations, papers, or studies in support of the claim that pitolisant “increases histamine levels in the brain.” Nor could we locate any discussion of the claim in any of the FDA review documents, and the FDA's word choice in the introductory paragraph is telling: “Pitolisant purportedly inhibits the negative feedback mechanism for histamine, resulting in increasing histamine release.” However, the EMA review cites an in vivo data point in rodents where pitolisant supposedly increased brain levels of t-meha, short for tele-methylhistamine. T-meha is not histamine. It is merely one of several metabolites that histamine breaks down to. The rodent study, as we shall detail, used a bespoke, unproven assay that tried to infer histamine levels from T-meha. The EMA reference says that the oral ED50 – the dose required to achieve 50% of the desired response in 50% of the population – was 1.6-3 mg/kg in rodents, which implies a human dose radically greater than the max dose on the label.

**FDA CDER Clinical Review**

1. Background

Pitolisant is a histamine 3 (H3) receptor antagonist and inverse agonist. Pitolisant purportedly inhibits the negative feedback mechanism for histamine, resulting in increased histamine release. Pitolisant may also stimulate release of histamine from presynaptic neurons and facilitate histamine synthesis. In addition, its actions on the H3 receptors are thought to lead to downstream release of dopamine, noradrenaline, and acetylcholine.

**EMA review**

In vivo studies showed that pitolisant enhanced the activity of histaminergic neurons as shown by the increase in brain levels of t-MeHA with oral ED50 values reaching 1.6-2.6 mg/kg in mice and 3 mg/kg in rats. In mice treated subchronically, the effect was similar and no tachyphylaxis was observed. In...
Comically, the entire claim that pitolisant increases histamine levels in the brain – the whole premise of its mechanism of action - is based on two dubious rodent studies from 2006 and 2007, one by Bioprojet scientist Xavier Ligneau and one funded by Bioprojet where Ligneau and Schwartz are co-authors. The red flags are numerous. First, both papers measure a histamine metabolite (T-meha) and not histamine, a questionable method with no evidence of its validity. One of these papers states that “t-meha levels [are] an index of histaminergic activity,” citing a 1991 paper by Schwartz, which we read and merely passes the buck by citing rodent studies from the 1970’s and early 1980’s. Our literature search going back decades failed to locate a single study demonstrating a correlation or index of histamine levels vs. t-meha, whether in rodents or humans.

*Both the 2006 and 2007 papers only used rodents and T-meha as an index for histamine (2006 below)*

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*Changes in Brain t-MeHA Level after Acute or Chronic BF2.649 Administration to Mice.* Administration of BF2.649 to mice elicited a dose-dependent and marked increase of brain t-MeHA levels, an index of histaminergic neuron activity. (Schwartz et al., 1991) Ninety minutes after oral administration, the maximal increase was by 91 ± 5%, similar to that elicited by ciproxifan (86 ± 4%), and the ED₅₀ was 1.5 ± 0.2 mg/kg p.o. (Fig. 6). Similar values were found with female OF1 and male C57BL/6J mice (data not shown). The study of the time course indicated that the increase elicited by 3 mg/kg was maximal after 60 min (119 ± 9%, in this experiment), with the level decreasing slowly and still being significantly enhanced after 4 h 30 min but no more so after 6 h (Fig. 7). Similar results were obtained in male Wistar rats with BF2.649 showing an estimated ED₅₀ value of 3 mg/kg p.o. on the t-MeHA index in cerebral cortex (data not shown). In addition, the effect on t-MeHA elicited by a 10-ng/kg oral dose of BF2.649 was not significantly modified after a 17-day chronic treatment with BF2.649 (Table 3) in mice.

1991 Schwartz paper (at right) cited above merely cites rodent studies from the 1970’s and early 1980’s

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Chart of t-meha levels in mouse brain after oral administration of pitolisant, as % of control

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The second red flag is that both rodent studies used a “supramaximal dose” of pitolisant in order to come up with a relatively modest increase in T-meha vs. the control animals – which of course also implies a supernormal human dose far higher than the max 35.6mg on the label. The 2006 paper used 1.5-2.5 mg/kg as the ED50 dose and the 2007 paper used 20 mg/kg. Both papers were in mice and show that ~20 mg/kg was necessary to achieve a ~90% increase in T-meha.

2006 paper: ~20 mg/kg to achieve ~90% increase in T-meha

2007 paper using 20 mg/kg: ~90% increase in T-meha in pitolisant mice (shaded) vs. control (white)

Fig. 6. Changes in brain t-MeHA levels in mice receiving BF2.649 in various dosages. Mice were sacrificed 90 min after oral administration. t-MeHA levels in treated mice are expressed in percentage of levels in control mice (133 ± 5 ng/g). Means ± S.E.M. of values from 18 to 24 mice.

Wild type mice Knockout mice with orexin deficiency to model narcolepsy

Even if Wakix increased histamine levels, Bioprojet admits it has no correlation with narcolepsy or sleepiness.
Even if there was evidence that pitolisant increases histamine levels in the brain, it wouldn’t matter as Bioprojet once published a study that unequivocally discredits the purported mechanism of action. The conclusions are devastating, as they showed no association between histamine levels and hypersomnia conditions such as narcolepsy, cataplexy, or sleepiness whether EDS or idiopathic hypersomnia, whether measured objectively via sleep tests or subjectively via ESS. The comprehensive 164-patient study measured correlation with biomarkers such as CSF (cerebrospinal fluid) histamine, histamine metabolites (T-meha), and hypocretin. Published in 2012 - years before they submitted pitolisant for EMA/FDA approval, at a point we think they’d written it off for failure – the paper was authored by the key figures in its scientific and clinical development: Yves Dauvilliers, who was the lead author and presumably principal investigator for HARMONY 1 and 3, and Bioprojet head Jean-Charles Schwartz.

*2012 paper funded by Bioprojet*

Normal Cerebrospinal Fluid Histamine and tele-Methylhistamine Levels in Hypersomnia Conditions

Yves Dauvilliers, MD, PhD\(^{1,2,3}\); Nathalie Delalée, MSc\(^{4}\); Isabelle Jaussent, MSc\(^{2,4}\); Sabine Scholz, MSc\(^{3}\); Sophie Bayard, PhD\(^{1,2,3}\); Mickael Croyal, MSc\(^{4}\); Jean-Charles Schwartz, PhD, PharmD\(^{1}\); Philippe Robert, PhD, PharmD\(^{4}\)

**Measurements and Results:** No between-hypersomnia group differences were found for CSF HA levels (median 708.62 pM extreme range [55.92-3335.50] in NC; 781.34 [174.08-4391.50] in NwC; 489.42 [177.45-906.70] in IH, and 1155.40 [134.80-2736.59] in Uns EDS) or for t-MHA levels. No association was found between CSF HA, t-MHA, or HA + t-MHA, sleepiness, treatment intake, and frequency of cataplexy. A slight negative correlation was found between age and HA levels. Further adjustment for the age revealed no significant HA levels difference between hypersomnia patients and controls.

**Conclusion:** CSF histamine and tele-methylhistamine did not significantly differ between patients with narcolepsy-cataplexy and other etiologies of non-hypocretin-1 deficient central hypersomnias; these measurements, therefore, are not useful in assessing the etiology or severity of centrally mediated hypersomnia.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443762/pdf/aasm.35.10.1359.pdf
The paper never mentions “pitolisant” but acknowledges that it contradicts the Bioprojet clinical trials already conducted, and further admits that the results negate their starting “hypothesis” that “CSF HA [histamine] and t-MHA [histamine metabolite] were…interesting biological markers of EDS.” The paper adds that it supersedes a previous study that showed an association, as this one used a newer “ultra-sensitive, ultra-performance assay…for the simultaneous analysis of HA and its major stable metabolite tele-methylhistamine (t-MHA) in CSF.” The paper cites “recent data” in monkeys that similarly showed no correlation.

Bioprojet-funded paper shows no association between histamine (left) or its metabolite (right) with various etiologies of excessive daytime sleepiness such as narcolepsy with and without cataplexy an idiopathic hypersomnia

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443762/pdf/aasm.35.10.1359.pdf
The paper is striking in its honesty, which we attribute to Bioprojet already having terminated pitolisant by 2012, given its omission in Bioprojet papers around that time which mention other “lead compounds” for its H3 receptor program. The paper even reframes the original 2007 rodent paper, which is the primary evidence that pitolisant increases histamine levels in the brain, stating that it showed that there was no difference in histamine levels between control mice and orexin mice bred to have narcolepsy. We paste the concluding section of the study below: that histamine is a “non-informative biomarker…to diagnose…etiologies of central hypersomnia” and that “from a clinical point of view” histamine levels are “not informative tools to differentiate etiologies of central hypersomnia or to assess the severity of centrally mediated hypersomnia.”

### Conclusions from Bioprojet paper shows no association between histamine and narcolepsy/sleepiness

Altogether, even if discrepancies exist between studies, CSF measurements of both HA and t-MHA appear non-informative biomarkers to diagnose and differentiate between etiologies of central hypersomnia with or without hypocretin deficiency. Our results may contrast with the positive clinical findings of the inverse agonist of the H3 receptor that enhance wakefulness in normal animals and decreases EDS in orexin/- mice and human narcoleptic. However, our present results were in agreement to those reported between orexin/- mice and WT mice showing normal cortical activity of HA neurons (assessed by measuring the cortical level of t-MHA) during the dark (active) period at baseline.

To conclude, we report the results of the first use of a method that provides a highly sensitive and selective quantification of both CSF histamine and its metabolite t-MHA in a large population of patients affected with narcolepsy-cataplexy, other etiologies of non-hypocretin-1 deficient central hypersomnia, and neurological controls. Being without significant difference between groups we believe from a clinical point of view that the measurement of CSF HA and t-MHA are not informative tools to differentiate etiologies of central hypersomnia or to assess the severity of centrally mediated hypersomnia. However,
The Bioprojet paper showing no correlation between histamine and sleepiness was a landmark finding and merited an editorial in the journal (SLEEP) in which it was published. The author, a neurology professor and leading scientist in sleep research, called it “a back to the drawing board moment” that undermined the “very seductive tale in which the protagonist is brain histamine.” He slammed the previous pitolisant studies and detailed “additional methodological concerns” with the now-discredited histamine hypothesis, concluding that the finding “is not at all surprising” and that “this should temper concluding that...histamine...is the principal arbiter of sleepiness in primary hypersomnias.”

*Editorial introducing the Bioprojet paper that undermines the entire pitolisant mechanism of action*
We find it stunning that the lack of correlation between histamine levels and narcolepsy is an open secret in Harmony/Bioprojet’s inner circle of founders, trial investigators, and key scientific advisors. CEO Jeff Dayno has previously highlighted Thomas Scammell on a HRMY earnings call, a neurology professor and sleep expert at Harvard Medical School. Scammell wrote a paper in 2019 which summarized supportive studies that undermine the histamine hypothesis, beyond the 2012 Dauvilliers/Schwartz paper. For example, he cites another paper – on which Dauvilliers/Schwartz are ironically co-authors – that found no difference in histamine or T-meha levels between narcolepsy vs. control patients.

Scammell 2019 paper rejects histamine link
Histamine: neural circuits and new medications
Histamine Is Not a Reliable Biomarker for Narcolepsy and Other Central Hypersonmias

furthermore, histamine levels did not correlate with subjective (Epworth Sleepiness Scale) and objective (Multiple Sleep Latency Test) measures of sleepiness or CSF orexin-A levels [85]. These results were in agreement with the normal cortical levels of tele-methyl histamine in orexin-/ mice compared with wild-type mice [20]. In a small number of patients with narcolepsy, CSF was collected again several months after the first sample; yet, histamine and tmHA levels showed no consistent change [86]. Altogether these data suggest that despite the increased number of HDC cells, extracellular histamine levels are likely normal in patients with narcolepsy.

...citing various studies showing no link to sleepiness
Histamine and tele-methylhistamine quantification in cerebrospinal fluid from narcoleptic subjects by liquid chromatography tandem mass spectrometry with precolumn derivatization

selective requirement to quantify these amines in human CSF. No significant difference was found in the mean±standard error levels of these amines between a group of narcoleptic patients (histamine=392±64pM, tele-methylhistamine=2431±461pM, n=7) and of neurological control subjects (histamine=402±72pM, tele-methylhistamine=2209±463pM, n=32).
Pitolisant’s pharmacokinetic profile is a disaster – bioavailability problems and blood-brain penetration
An inability to increase histamine levels and histamine’s irrelevance to narcolepsy and sleepiness are the least of the problems with pitolisant’s purported mechanism of action. A more fundamental issue is its lack of bioavailability, which refers to the percentage of active drug that gets into the blood, without which an insufficient amount is available for a therapeutic effect. Pitolisant is subject to extensive first-pass metabolism by CYP3A4, which means most of the drug is lost by metabolism in the liver and gut before it gets into general circulation, thereby preventing enough of it from getting to the target organ, i.e., the brain. We believe Harmony is aware of pitolisant’s bioavailability problem and that their claim of 90% oral bioavailability/absorption in the package insert is simply false. In addition, their pre-clinical studies claiming 85% and 37% bioavailability in mice and rats, respectively, are erroneous.

**Wakix package insert claims 90% bioavailability**

**Absorption**

The median time to maximum plasma concentration ($T_{\text{max}}$) of pitolisant is 3.5 hours (2 to 5 hours). The oral absorption of WAKIX is around 90%.

**FDA CDER Tertiary Pharmacology/Toxicological Review** – 85%/37% bioavailability in rodents

| Table 8. Serum Concentrations and Bioavailability of Oral and IV Pitolisant in Mice and Rats |
|---|---|---|---|
| Species | Units | Oral | Intravenous |
| | | $C_{\text{max}}$ | AUC | $AUC_{\text{IV}}$ | $T_{\text{max}}$ (min) | $T_{\alpha}$ (min) | Bioavailability Ratio $AUC_{\text{oral}}/AUC_{\text{IV}}$ |
| Mouse | nmol or nM/L or ng/mL | 1994 ± 222 | 7916 | 9449 | 13 | 126 | 0.84 |
| | ng/mL or h ng/mL | | | | | | |
| Rat | nmol or nM/L | 310 ± 73 | 764 | 2082 | 3 | 49 | 0.37 |
| | ng/mL or h ng/mL | 92 ± 22 | 226 | 616 | | |

Data are presented as mean ± standard error. Values obtained from 6 animals per group except for oral treatment in rat (n=12). Mouse $C_{\text{max}}$ was measured at 1 h; rat $C_{\text{max}}$ was measured at 15 min.

[Excerpted from NDA211150, Pharmacokinetics Written Summary; page 19]

In contrast to the 90% figure claimed by Harmony, pitolisant’s actual bioavailability is a mere 1.5% in mouse, 1.5% in rat, and 27% in monkey. These figures are consistent with data we received from several large pharma companies, who cited lack of bioavailability as one of many fatal flaws that led to the termination of their H3 receptor antagonist/inverse agonist programs, and whose in-house analysis of pitolisant specifically concluded that it suffers from the same issues. We hired a pharmacology consultant, who has conducted hundreds of pharmacokinetic and bioavailability studies, to examine Bioprojet/Harmony’s methodology and claims. The conclusions in the 60-page report were received were damning and we interpret them as indicating that the claims are fraudulent with red flags, discrepancies, contradictions, and omissions that suggest an intent to mislead the FDA. The consultant further pointed to a telling statement in the EMA review: “the absolute bioavailability of pitolisant has not been determined.”

**EMA review of pitolisant, 2015**

According to a mass-balance study conducted in 6 healthy male subjects dosed with 20 mg in fasting state, a mean recovery of at least 88% of administered radioactivity was recovered, primarily from urine (approximately 63%) with approximately 25% of the dose excreted through expired air and a small fraction (<3%) recovered in faeces. The absolute bioavailability of pitolisant has not been determined.
The consultant’s review details a pattern of flagrant flaws that led to the “vastly overestimated bioavailability”: 1) the Bioprojet studies were plagued by a dubious methodology and errors, such as using radiolabeled pitolisant but failing to correct the circulating levels of radioactivity for the concentration of inactive pitolisant metabolites, as the correction would result in only 1.5% bioavailability vs. the 37-85% claimed; 2) Bioprojet’s data shows that they knew the importance of correcting for “the fraction of metabolized drug within the total pool of radioactive mix (comprising both active and metabolized pitolisant),” suggesting that the errors were not accidental; 3) the human mass balance studies were equally suspect and “failed to consider active vs. inactive drug when calculating oral bioavailability in humans”; and 4) the failure to conduct standard bioavailability assessments such as “IV vs. oral AUC comparison…is a red flag.”

Excerpts from pharmacology consultant’s review of bioavailability claims – see Appendix

“The package insert for Pitolisant states that the absorption is >90% in human subjects. The package insert is then referenced in other publications to support the claim of high 90% bioavailability of Pitolisant in subsequent publications. However, neither of these statements are correct since the concentration of metabolites were not accounted for in human mass balance studies […] According to the EMA, the absolute bioavailability of Pitolisant “has not been determined”. (EMA 2015, p 34). This is the correct statement. The method by which Harmony determined bioavailability was disclosed in a priority review (Mehta 2018) (pg 7) where they first state that WAKIX has an oral absorption of approximately 90%... because after a single oral dose approximately 90% of the dose was excreted in the urine (2% unchanged parent Pitolisant and 98% inactive metabolites). There are numerous problems with the determination of F% by mass balance […] Thus, again, Harmony failed to consider active vs inactive drug when calculating oral bioavailability in humans – the same mistake that they were called on in the preclinical studies […] The fact that the IV vs oral AUC comparison is not made is a red flag. But the original claim of 90% recovered in the urine is ALSO incorrect.”

Source: Bioavailability analysis commissioned by Scorpion Capital
In addition to a general lack of bioavailability, pitolisant’s purported mechanism of action is doubtful due to blood/brain barrier permeability and CNS uptake. The blood/brain barrier is a major obstacle in the development of CNS drug delivery and a class problem with H3 receptor antagonists/inverse agonists – one of many impediments conveyed to us by scientists involved in failed H3 receptor drug programs at several large pharma companies. The only CNS uptake data we can locate for pitolisant is from rodent studies in the 2000’s – no human data appears to be available. Our pharmacology consultant reviewed the data and found it suspect and troubling. First, the study failed to use a standard methodology for measuring CNS uptake in rodents called quantitative whole-body autoradiography (QWBA). The study instead homogenized the brains after sacrificing the mice, presumably centrifuging to measure ng/g concentrations. Second, the data is highly suspicious, as it shows brain levels of pitolisant that appear ~20X higher than those in the blood – the opposite of the typical pattern.


“In (d), tiprolisant and modafinil concentrations in plasma and brain, determined by HPLC/MS, are depicted…”

Brain concentration (top) is ~20X higher than in blood (bottom)
Our pharmacology consultant highlighted how unusual it is for brain concentration of drug to be this high versus the blood: “I have done hundreds of biodistribution studies and literature reviews and I have never seen this.” She consulted a second expert who also found the data odd. The pattern is repeated in two additional data tables in the FDA CDER pharmacology/toxicology review, which shows brain (ng/g) concentration 15-fold more concentrated than in the blood (ng/mL) – the data is suspect even without correcting for blood and CSF volumes. We note another striking discrepancy: both brain and plasma levels are shown as higher with the lower dose (10 vs. 20 mg/kg), which makes no sense.

**Pitolisant data shows a highly unusual 15-fold higher concentration in brain than in blood**

Table 26. Pitolisant Levels in Serum and Brain Tissue 15 Minutes Post-Dose Versus After Premature Death Following I.v. Administration of Pitolisant in Rats.

<table>
<thead>
<tr>
<th>Dose</th>
<th>BF2.649 ng/mL SEM</th>
<th>Dose</th>
<th>BF2.649 ng/g SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg</td>
<td>714.87 90.7</td>
<td>10 mg/kg</td>
<td>29756.17 2733.34</td>
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<tr>
<td>20 mg/kg</td>
<td>547.00</td>
<td>20 mg/kg</td>
<td>24422.50</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Rats Sacrificed at the 15-min Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non convulsing</td>
</tr>
<tr>
<td>n = 8</td>
</tr>
<tr>
<td>Convulsing</td>
</tr>
<tr>
<td>n = 12</td>
</tr>
</tbody>
</table>

Table 28. Serum and Brain levels of Pitolisant and major metabolites in Sprague-Dawley Rats After Single Oral Dose of Pitolisant at 400 mg/kg

<table>
<thead>
<tr>
<th>Dose 400 mg/kg, p.o. rats</th>
<th>Analyte (ng/mL in serum or ng/g in brain tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF2.649</td>
<td>BP2.951</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>Non convulsing</td>
<td>n = 8</td>
</tr>
<tr>
<td>Convulsing</td>
<td>n = 12</td>
</tr>
</tbody>
</table>

| Brain    | Non convulsing | Mean | 3769 | 15 | 1270 | 10236 |
|          | n = 8          | SD   | 1705 | 0  | 361  | 3049  |
| Convulsing | n = 12 | Mean | 8916 | 18 | 1523 | 13766 |
|           | SD           | 4892 | 5    | 273  | 1358  |

[Excerpted from NDA211150, Study Report B115-BF2.649; page 12]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211150Orig1s000PharmR.pdf
In order to concoct some evidence in man of pitolisant’s purported mechanism of action, Bioprojet funded a 2020 PET brain imaging study (n=6 healthy adults) to show that the drug “produces a high occupancy of H3 receptors” in “nine brain regions of interest” – that is, that the drug binds to the H3 receptor. The study is as dubious as the bioavailability and CNS uptake data. Our pharmacology consultant engaged a longtime PET expert to review methodology and data, who has conducted identical studies, who found it so unusual as to state that he has “never seen data like this.” The concerns are detailed in the report we received, which include: 1) a failure to correct the H3 receptor antagonist radioligand (the foundation of the study) for metabolism, which artificially inflates the results; 2) troubling patterns in the data that “call into question the accuracy of the information presented in the PET study.”

**Pitolisant data shows a highly unusual 15-fold higher concentration in brain than in blood**

**Exploring occupancy of the histamine H\(_3\) receptor by pitolisant in humans using PET**

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**Excerpts from review of the PET study by our pharmacology consultant and a PET expert – see Appendix**

“The fraction of active C11-GSK189254 was not corrected for metabolism and this fraction should be part of the corrections mentioned above […] Another problem with these data was pointed out by my PET expert colleague. He has done many C11 studies, and he was surprised by the data exemplified in Figure 11.1 in terms of the lack of variability change over time…he said he has never seen data like this. This then calls into question the accuracy of the information presented in the PET study. He said he would never trust the accuracy of PET data beyond 45 min.”
We further note that the time to maximal effect on the EDS endpoint (excessive daytime sleepiness) undermines pitolisant’s supposed mechanism of action, which presumes an increase in brain histamine resulting in wakefulness. In the 12-month HARMONY 3 open-label clinical trial, the maximal effect isn’t reached until 6-9 months of daily administration – for both de novo patients (9 months) and those already exposed to the drug (6 months). This led our pharmacology consultant to comment: “These results are strange because the increase in histamine levels in the brain should be immediate and so the therapeutic effect should also be rapid (and should not require 6 months to reach a maximum effect). If one takes an antihistamine (H1 blocker) such as Benadryl, the somnolent effect occurs at peak plasma levels – approximately 30 minutes later. One does not need to take them for 3 months to achieve this.”

**Excessive daytime sleepiness (EDS) score per ESS in HARMONY 3**

Figure 3. Epworth sleepiness score over 12 months in the total intention-to-treat population, without replacement of missing values. Data are the mean (±SE) and (95% CI) of number of patients (n).

Figure 4. ESS score over 12 months in the subgroups of de novo and previously exposed to pitolisant patients intention-to-treat, without replacement of missing values. Data are the means (±SE) and (95% CI) of values.

The efficacy data for ESS and cataplexy shown in the HARMONY 3 paper indicates troubling discrepancies. First, the time to maximal effect is 6 months for ESS and 9-12 months for cataplexy, contradicting the results in HARMONY 1 and CTP which showed that the vast majority of the effect is immediate, within the first couple of weeks of treatment. Second, the ESS score reductions by month 3 and thereafter in the ITT group are implausibly high, given the large number of patient withdrawals by that point due to lack of efficacy. We note that the results are inflated to begin with due to selection bias, as the trial switched over patients from the French Compassionate Use Program.

ESS and cataplexy results contradict time to maximal effect in prior trials and are otherwise implausible

Figure 3. Epworth sleepiness score over 12 months in the total intention-to-treat population, without replacement of missing values. Data are the mean (±SE) and (95% CI) of number of patients (n).

Figure 5. Frequency of episodes of generalized and partial cataplexy over time for the whole ITT population. Data are the means (±SE) and (95% CI) in 43 patients with cataplexy who completed the diaries until the 12-month visit.

Harmony’s sales are dependent on a handful of physicians, paid via a speakers program that ex-employees described as a blatant kickback scheme.
We interviewed 14 former Harmony executives and employees, a majority of whom were sales/territory managers in large regions across the country. They consistently described the company’s sales and business model as being dependent on a small number of high-volume prescribers – “whales” who are typically paid promotional speakers, which the ex-employees described as a quid pro quo and inducement for doctors willing to write large numbers of Wakix prescriptions. Speaker’s programs which constitute kickbacks or rewards are flagrantly illegal, resulting in high-profile indictments of executives of companies – Insys, for example, being a recent poster-child where the CEO, physicians, and others were sentenced to prison. Fraudulent speakers programs are the target of heightened scrutiny, as evidenced by a 2020 “Special Fraud Alert: Speaker Programs” issued by the HHS Office of Inspector General. HRMY’s program is a textbook case of the red flags listed in the memo.

**HHS OIG Special Fraud Alert, 2020**

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**Special Fraud Alert: Speaker Programs**

November 16, 2020

I. Introduction

This Special Fraud Alert highlights the fraud and abuse risks associated with the offer, payment, solicitation, or receipt of remuneration relating to speaker programs by pharmaceutical and medical device companies. For purposes of this Special Fraud Alert, speaker programs are generally defined as company-sponsored events at which a physician or other health care professional (collectively, “HCP”) makes a speech or presentation to other HCPs about a drug or device product or a disease state on behalf of the company. The company generally pays the speaker HCP an honorarium, and often pays remuneration (for example, free meals) to the attendees. In the last three years, drug and device companies have reported paying nearly $2 billion to HCPs for speaker-related services.¹

Source: https://oig.hhs.gov/documents/special-fraud-alerts/865/SpecialFraudAlertSpeakerPrograms.pdf
An ex-territory manager for a large northeast region stated there was “no question” that reps had to dangle the speakers program – “100%, absolutely.” He indicated the pressure came from Harmony’s management, but that “they’ve never going to put it in writing, but make no mistake, it was very clear.” Describing a textbook inducement, he implied that it didn’t matter if “they’re good speakers…get them on there,” adding that “they’re not going to put a low-volume scientific speaker in there” and that is has to be “somebody who’s…using a lot of the drug.” An ex-manager in another region corroborated the color, stating that successful territories depended on speakers with an unspoken quid pro quo.

“It was very clear” to dangle the speakers program; “no question”
Q: “Did they ask you to dangle the whole consulting speaker’s program to anyone, like the biggest prescribers? Did they tell the salesforce to do that?”
A: “Oh, 100%, absolutely. So, I actually introduced them to [top prescriber name redacted]…there’s no question. Look, they’re never going to put it in writing but make no mistake, it was very clear, if there are high prescribers, then let’s see if we can get them on the speakers bureau. If they’re good speakers, great. But more important, that you get them on there.”
Q: “Where was this direction coming from? From the CEO? Or VP or whatever?”
A: “It all came down through the sales, probably from the COO downwards but, again, honestly, very nuanced. It’s not a secret that they would want high volume—they’re not going to put a low-volume scientific speaker in there. It’s going to have to be somebody who’s promoting - using a lot of the drug, and if they’re a great speaker, even better.
Q: “Was there any kind of understanding with the doctor in terms of volumes to be on the speaker’s program or was that understood?”
A: “I think it’s more a given. I’m trying to think if I know any other speakers there. It would never be explicitly said, but it’s kind of an understood given, and then the people tend to self-select for themselves.” – Ex-Harmony territory manager for a large region in the northeast

Successful territories depended on speakers with an unspoken quid pro quo
“So, it did fall off…my performance did slip off for that quarter, but in previous quarters, I had done well. Yes, there were a lot of representatives that their performance had fallen way off. My question is, the very successful territories had speakers in them and, you know, when you pay somebody to do talks for you, you tend to get—it’s harped upon, it cannot be quid pro quo but, let’s be honest, to a degree, you pay somebody a stipend to do a talk for you, and you continue to do that, they tend to look to use your drug. I’m not saying that they’re going to use it in inappropriate places, but they look to use your drug more frequently. So, those people were successful.” – Ex-Harmony territory manager for an eastern state

Source: Scorpion Capital consultation calls with experts
We quote three different ex-territory managers below. One stated Harmony’s top prescriber in the US “is a complete whore” and that he would “say it to his face” as “we hang out socially and so forth.” A second said whales are “going to carry” your quota, and that there was a large prescribing disparity between whales and non-speakers, who would barely touch the drug. A third stated that there was about one speaker per territory – “pretty much everybody had a speaker” – who drove the volume.

Alleged top prescriber “is a friend of mine” and is a “complete whore”
“There is another board-certified sleep specialist. This guy is a complete—forgive my language—whore when it comes to the pharma industry...Their number-one prescriber, number one in the United States for a period, is a friend of mine...We hang out socially and so forth. His name is [redacted]. I would call it to him and say it to his face. Feel free not to quote me on it, but he’s a complete whore when it comes to the industry.” – Ex-Harmony territory manager for a large region

Whales are “going to carry” your territory’s quota; large prescribing disparity between whales and other docs
“Yeah, you had a lot of—there are some offices that just would pump things out and just a lot of scripts, a lot of volume, and then you would have a lot of people that—we called them "dabblers—" they would just kind of ones and twos here and there. It was kind of like a disparity, to be honest with you. You either had a big whale—that’s what we call them, like, hey, you’ve got a whale. They’re just going to carry you. The problem is if a whale drops off now, now you’ve got a problem because you’ve set a precedent already, and now you’ve got somebody that, for whatever reason, stops. There are only so many narcolepsy patients. It’s a rare disease, so at some point, you have to feel like these providers, these physicians are going to run out of narcolepsy patients because you would go back and look for your narcolepsy patients that might need help, and I think at some point, the fear is always that they, how do you continue to do this? So, a lot of territories have got a big whale. Some of them would drop off, and then the ones that had a whale, there was a disparity between them.” – Former territory manager in a large Midwest state

Generally each territory had about one speaker who drove the volume
Q: “So, the big prescriber that you had in [small city redacted], was that somebody in the speaker's program or a consultant or somebody who participated in the trial?”
A: “Yeah, he did speak for us”
Q: “Was he the only speaker in the territory?”
A: “Yeah, but that's not unusual. There's usually one speaker per territory at this company, anyway. Pretty much everybody had a speaker. I had a speaker in my territory. Every territory had one key person that was a speaker that could cover that territory and surrounding areas.” – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
A fourth ex-territory manager provided more detail on the extreme prescribing disparity, indicating 150-175 potential prescribers in the territory – of which “I had 90 I saw on a rotating basis” – but the one who was a speaker drove 25-30% of the quarterly referrals. The top two comprised about a third to one-half of the total.

An example region had 150-175 potential prescribers but a single whale – a speaker - drove 25-30% of the scrips; two prescribers comprised ~1/3 to 1/2 of the scrips
Q: “How many doctors did you call on in your territory?”
A: “I think my list was about 150 or 175. I would say maybe I had 90 I saw on a rotating basis.”
Q: “And how many did you get to write the prescription at least once? And then what percentage of those ended up being consistent writers or whales?”
A: “I had very few whales in my territory, which made it even more difficult for me, even though I did well.”
Q: “So, who was your biggest prescriber? How many scripts was that?”
A: “My biggest prescriber was actually a doctor who toggled between [hospital name redacted] and [city redacted].”
Q: “How many was he writing? How many scripts or how many patients did he have on Wakix?”
A: “I would say by the time I left, so my goal was usually around 20 per quarter, which is astronomical when you’re talking about rare disease, that’s a lot. So, he was probably writing maybe 5 or 6 of those 20 a quarter.”
Q: “And then, how about your next biggest? So, he’s writing about 20 a year. Who was your next biggest one?”
A: “My next biggest one was one of the doctors at [hospital redacted]. He was at like maybe 2 or 3 a quarter.”
Q: “So, you basically had one giant whale, and then you had another one that was like a fraction of that, then you had a bunch that would be a few a year?”
A: “Yup, basically.”
Q: “So, is the first person, is he a speaker?”
A: “Dr. [redacted] was a speaker, correct.”

– Ex-Harmony territory manager for several states in the Northeast

Source: Scorpion Capital consultation calls with experts
A fifth former territory manager described how speakers put a supernormal number of patients on the drug out of the gate, with 8-10X the volume of typical doctors – “one of my speakers...he just, god, every day he put two people on...he wrote 38...in the first quarter...and I told you four or five is big.” He chuckled when he indicated that it’s a “pretty safe assumption” that only speakers tend to prescribe the drug in such massive volume – and even admitted that speakers program abuses “could be potentially criminal...it would be criminal.”

**Speakers put supernormal number of patients on the drug right away; 8-10X a normal figure**

A: “Yeah, we blew it out. I, particularly, really blew it out. I had one of my speakers, [name redacted], he just, god, every day he put two people on. He wrote 38, I think is what my memory serves, in the first quarter. And I told you four or five is big. He wrote 38 in one quarter. My first bonus check was over 50k for one quarter. The second quarter, same deal. And then, he ran out of patients.”

Q: “Are you still in touch with him? How many patients does he have now?

A: “...I don't know if he knows, to be honest. Not too many. I know the rep that ended up with him, and he told me he was writing about one or two a quarter for him.”

Q: “Was that common that there was this big spike, and then it came down?”

A: “Yeah, because you have something new. You had a disease state that's very difficult to treat. So, they're looking for something else, and yeah, when we launched, they put them on, and then they came back down to earth.” – Ex-Harmony territory manager for an eastern state

“**Pretty safe assumption**” that only speakers tend to prescribe massive volume

A: “Reps talk a lot with each other. I talk to people from all over the country...it could be potentially criminal. It would be criminal. But I didn’t know that.”

Q: “I had heard there was some of that going on. That's why I'm asking. It sounds like the only people that prescribe massive volumes of this drug are speakers.”

A: “Yeah, I assume that's what it was....[chuckles]...yeah. Yeah, I'm not privy to—we just didn't have that information, but yeah, I would assume that's a pretty safe assumption, especially at this point.” – Ex-Harmony territory manager for an eastern state

Source: Scorpion Capital consultation calls with experts
A sixth ex-territory manager described the brazen nature of Harmony’s conduct – “there was always an overhanging threat of being put on a disciplinary plan if you didn’t get a certain amount of speaker programs within your territory.” He stated there were “certain quotas” that were “pushed down from upper management” and that doctors “were more willing to write if they were promised” a “speakership or sponsorship program” – “I don’t know if it was a quid pro quo but it felt like...where a doctor suddenly popped up as a primary speaker and he or she would write of a lot of prescriptions.” Giving away the rig, he added that “then they were taken off the speaker list and all of a sudden the prescriptions dropped...that always raises an eyebrow – is there a quid pro quo....”

“Threat” of being disciplined if not enough speaker programs; quid pro quo; prescriptions correlated to being put on or off a speakers program

A: “Yeah, there was always an overhanging threat of being put on a disciplinary plan if you didn’t get a certain amount of speaker programs within your territory. Those were difficult to get in some areas. The doctors also were more willing to write if they were promised and actually a speakership or sponsorship program. In some areas, I don’t know if it was a quid pro quo, but it felt like that in some areas where a doctor suddenly popped up as a primary speaker, and he or she would write a lot of prescriptions. And then they were taken off the speaker list, and all of a sudden, the prescriptions dropped down. So, there was that that always raises an eyebrow—is there a quid pro quo with certain doctors that makes them write prescriptions because they’re being paid for a program that they—”

Q: “You said there’s a threat of disciplinary action if a rep didn’t get enough doctors in the speaker program? What was that about?”
A: “Basically, there were certain quotas that had to be attained, and this was down from upper management; it was pushed down. They expected a certain amount of speaker programs in each territory per quarter. Unfortunately, those were hard to come by as we got a little bit older with the company simply because you have one doctor that goes out and does a program for a couple of counties or a couple of towns, and you invite that group to try to get back again. They’re not really willing to do that. They’ve seen the program once, they’re satisfied with the program, or they get enough information online. The ones that did attend were…and then some doctors actually came, and they actually said, I came because you picked a nice restaurant or I came for the steak, which was, in retrospect, a little insulting when you’re trying to get these guys to get them educated about the product itself.” – Ex-Harmony territory manager for a large region in Florida and another state

Source: Scorpion Capital consultation calls with experts
The former territory manager continued that there was “unspoken pressure” to remove doctors from the speaker’s program “if they weren’t filling prescriptions.” He shared an example of a doctor in his territory who “was underwhelming as far as writing prescriptions” and was “taken off the list” – “it was always felt that that was the reason why the doctor was taken off the speaker’s program.” He replied “yes, yes, it was” when we asked if this dynamic was common across other territories. When we asked where the pressure came from, he stated it was “a level or two above where my manager was,” which we interpret as meaning VP or C-level, based on our sense of Harmony’s organizational structure.

“Unspoken pressure” to take docs off speakers program if not writing enough prescriptions; common across territories; pressure allegedly came from upper management
Q: “Were there any quotas about the number of doctors that became speakers? In other words, you’ve got to get enough doctors to write enough scripts so that they actually get bumped into the speaker’s program. Any color around that or pressure?”
A: “There was some unspoken pressure that if a doctor was a speaker and they weren’t filling prescriptions, they would be taken off the program. That was not communicated between the doctors and the company, but, in my case, I did have a doctor that was underwhelming as far as writing prescriptions; very excited to jump on board and do a speaker’s program but just wouldn’t write prescriptions for his patients. So, he was actually asked to be taken off the list. It was never because you’re not writing prescriptions. We never said that; we never brought that to their attention, but it was always felt that that was the reason why the doctor was taken off the speaker’s program."
Q: “Is that pretty common across territories? Was that dynamic pretty common across other territories?”
A: “Yes, yes, it was.”
Q: “And where was this coming from? Like the VP of sales, the CEO? Who was driving this pressure?”
A: “I really can’t pinpoint exactly where it came from. I can only surmise and make a guess, and I hate to do that to put anyone—I don’t want to put anyone in a corner. But it was probably a level or two above where my manager was.”
Q: “So, like the VP Sales?”
A: “Yeah, again, I wouldn’t put it on one person’s shoulders. I think it was multiple people.”
Q: “On the management team?”
A: “From the management team, right.” – Ex-Harmony territory manager for a large region in Florida and another state
When we asked if the speaker’s program was basically an inducement, the ex-manager replied “absolutely, 100%” and “100% exactly,” referring to the “whale” speaker in his territory. He further added that the doctor rarely even did speaking engagement – “he turned down almost every speaking engagement that I ever offered him.” When we asked if he was being paid as a speaker but not actually speaking, the ex-employee replied “absolutely correct,” and even explained that the doctor “was horrible…he was absolutely horrible…a complete disaster” when he had him do a talk.

“Absolutely 100%” that the speaker’s program was basically an inducement to write prescriptions

Q: “Were there doctors that the company or people knew, you know, these whales, where it’s all about the speaker’s program, writing scripts left and right?”
A: “Yes. The guy that I referenced that I had, absolutely, 100%.”

Q: “[speaker name redacted]?”
A: “100%. Exactly, yeah. I feel bad. I kind of like [speaker name redacted].”
Q: “What leads you to have that opinion?”
A: “Because he speaks for every— he’ll blow out any new drug that comes to market because he wants to be considered a speaker. And here’s the really crazy part to that, he turned down almost every speaking engagement that I ever offered him. The only ones he would do would be miles from his home. He didn’t want to travel. He did well. I think he’s got 6-8 different offices. He’s in [redacted], he’s in [redacted], and he’s in [redacted]. He’s making a really nice living. So, I think he literally just wanted to be a speaker, so it was like—”
Q: “So, [redacted] was being paid as a speaker, but you’re saying he wasn’t really speaking that much?”
A: “Absolutely correct. And he was horrible. He was absolutely horrible. I had him do a talk when we were in covid virtually, and [long anecdote redacted]. It was a complete disaster. He was horrible. But yeah, he’d turn down every—he had no interest. And then a guy that I really liked in California, the Bay Area, he’d do 6 to 8 talks for me in a row, like consecutive days, he’d spend the weekend. If he wanted to hustle, I could pay him, I guess, probably about two grand a talk. But [redacted] wanted nothing to do with it. He just wanted to be a speaker.” – Ex-Harmony territory manager for a large region in Florida and another state

Source: Scorpion Capital consultation calls with experts
>Off-label marketing prescribing allegedly drives 40% or more of Harmony’s prescriptions
Ex-territory managers and those in a field reimbursement role described a vast off-label prescribing scheme as key to Harmony’s sales. The Wakix label is clear and specific, stating as follows for “INDICATIONS AND USAGE”: “WAKIX is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.” Patients must have narcolepsy, and if so, Wakix may be prescribed for 1) EDS and/or 2) cataplexy. However, narcolepsy is extremely rare, and narcolepsy with cataplexy is a small fraction of that number. A recent epidemiological study estimated the incidence of narcolepsy at ~40 per 100,000 or ~130K in the US (0.04%); another pegged narcolepsy with cataplexy at 4.87 per 100,000 (.005%), or 16K – in other words, only 12% of narcoleptics have cataplexy.

**Wakix label**

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*Epidemiological studies on prevalence of narcolepsy (39 to 43 per 100K patients, per first study, 2020) and narcolepsy with cataplexy (4.87 per 100K, per second study, 2019)*

Prevalence of narcolepsy and other sleep disorders and frequency of diagnostic tests from 2013–2016 in insured patients actively seeking care


Given the small number of narcoleptics and even smaller number of those with cataplexy, former employees allege that Harmony is dependent upon a strategy that illegally promotes Wakix for 1) excessive daytime sleepiness even if there is no narcolepsy; and 2) incentivizes territory managers (via a highly unusual comp plan) and high-volume prescribers (via the speaker’s program) to falsely indicate cataplexy symptoms even if none are present, in addition to misrepresenting that reimbursement requirements have been met, like step-edits that require a patient to first fail various generics or other medications. One ex-territory manager explained it as a textbook off-label scheme: “the trick was to get it covered under cataplexy…now, we market it for – I don’t know what we said….” He described a wink-wink game where reps coach or cajole the doctor to indicate cataplexy by “really stretching it…so, you get into games like that….”

*The trick was “to get it covered under cataplexy”*

“*And the key to that was if it was cataplexy, you could get it covered…so, the trick was to get it covered under cataplexy because then you can reasonably get the $25 copay. Now, we market it for—I don’t know what we said…”*— Ex-Harmony territory manager for a large region in the southeast across two states

*Reps playing “games” and a wink-wink to get docs to falsely diagnose cataplexy symptoms*

A: “*Then you get into a game as a rep of cataplexy, and you're really symptoms of cataplexy. Well, you ask the physician; yeah, I don't see cataplexy very much. And then you're like, Oh, yeah, doctor, you don't see their hand shaking or their eye quivering—and you're really stretching it because cataplexy gets covered on most insurance plans.”*

Q: “I see. There's kind of like a wink-wink thing with the doctors where they are basically diagnosing cataplexy just to be able to write the script?”

A: “Yeah, because it gets covered. If it's cataplexy, it has better coverage. **So, you get into games like that.** Narcolepsy is tricky. There are some people out there, some patients that just suffer tremendously from it. But we're talking 200,000 patients in the U.S., supposedly.” – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
When we asked ex-territory managers if Harmony and its prescribers were playing any billing or coding games, ex-sales reps replied “the biggest one was cataplexy…that was your best go-to…the problem was the patient doesn’t have cataplexy.” The rep was unusually candid with us, admitting that he engaged in the practice: “I’ll be honest…I really tried to get those doctors to recognize cataplexy in patients…are you sure the patient doesn’t have cataplexy?” He indicated that Harmony pushed sales reps to engage in this conduct, under the guise of “speakers and experts tell[ing] us as a salesforce” that “you really need to talk with your doctors about cataplexy because they might be missing it.”

The biggest billing/coding games “was the cataplexy” – “that was your best go-to”; reps admitted to us they do it

Q: “Were there any billing or coding games?”
A: “The biggest one was the cataplexy. If you coded the patient narcolepsy with cataplexy, that was your best go-to. The problem was the patient doesn’t have cataplexy. So now the discontinuation or is diagnosing cataplexy because that’s how you got it covered.”

Q: “How often was that happening?
A: “I don’t know nationwide how often that was happening, but I know for me, I’ll be honest and transparent, I really tried to get those doctors to recognize cataplexy in patients. Are you sure the patient doesn’t have cataplexy?”

Q: “It sounds like you were asking them to recognize the subtle signs of it, in case it was that.”
A: “Right, right. I always was just like, hey, make sure you’re looking out for signs of cataplexy because it was true. The company used to tell us that there’s more cataplexy out there, and we had speakers and experts tell us as salesforce, there’s more patients out there with cataplexy than what doctors are recognizing, and so you really need to talk with your doctors about cataplexy because they might be missing it. I took that approach. Just make sure you’re not missing it. I don’t want you to code anything inappropriately; I’m not going to do that. I make plenty of money. I don’t need to go down that path of loopholes and all that. I don’t want to get fired. I stay on the straight and narrow compared to a lot of people. It’s just really educating myself on what are those signs of cataplexy and then trying to have doctors, especially ones that don’t have a lot of patients, look for those signs.” – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
When we asked if he observed any unethical conduct by Harmony’s management team, he replied that “there’s always pressure...they put reps in a very awkward position...you want to make money, and not that I would do it, but like the whole cataplexy thing, for instance....” He added that “I’m glad to be out of pharma now, that’s all I could say...the way that they compensate, you have to be a very ethical person....”

Pressure from the company for reps “to do the whole cataplexy thing”; “put reps in a very awkward position”

Q: “Did you observe any unethical or other things that gave you pause by the management team, the CEO, the company’s conduct, things you might have been asked to do as a rep?”

A: “There’s always pressure from these companies, and I’m not saying Harmony specifically, but the way that they raise your goals and do your commission, they put reps in a very awkward position.”

Q: “What do you mean? What was awkward about it?

A: “Well, you want to make money, and not that I would do it, but like the whole cataplexy thing, for instance. Or specialty pharmacy. I have seen staff in this industry—like, I’m glad to be out of pharma now, that’s all I could say. The way that they compensate, you have to be a very ethical person, which I consider myself to be, but the way these companies—all the pharma companies—compensate and the way that they change your commission structure... – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
When we asked another ex-territory manager if there were verbal, non-written instructions to the sales team to encourage off-label prescribing, he replied that it was to use “the vagueness of narcolepsy…so look for it…gray areas, like once you get that low-hanging fruit…start expanding…you gotta expand the diagnosis of narcolepsy.” We emphasize that Wakix is not indicated as a treatment for narcolepsy: it is only approved for two symptoms - EDS or cataplexy - in patients who have narcolepsy. It appears that reps would latch onto a patient with narcolepsy and then try to get the physician or their office to expand the diagnosis to cataplexy – even if the patient didn’t have it – to “comply” with the label. The rep was clear: “Is it unethical? Yes it is.”; “Yes absolutely, we were told to broaden the scope outside the box” – that is, the label; “Yes, that’s definitely off-label for sure. 100%. Did we ever read that in writing? No. Absolutely not.”

Alleged strategy is to push off-label prescriptions for sleepiness in the absence of narcolepsy; company told reps to exploit “vagueness of narcolepsy” to push physician to diagnose it even when it’s not there; “gray areas”

Q: “What were other instructions like that, that they gave the sales team that were verbal and never written? I’m just curious.”

A: “The vagueness of narcolepsy, saying for CPAP, it’s 30% of patients that fail CPAP are narcoleptic. I have no idea where they got that number from. Thirty percent of CPAP failures, everybody failed CPAP. CPAP sucks. So, somehow, they came up with the number 30%. Tell your physicians that 30% of all CPAP failures are narcoleptic patients, so look for it. Gray areas like, once you get that low-hanging fruit, as I mentioned before, start expanding. You gotta expand the diagnosis of narcolepsy. But the insurance companies are smart to that. You must have a certain amount of non-REM or failed REMs.”

Q: “So, they were basically instructions from the company to get the doctor to kind of suggest that the patient had narcolepsy when they may not have it—just to be very liberal with the definition of it?”

A: “Yes. If you think about it, is it unethical? Yes, it is. However, we weren’t treating narcolepsy; we were treating excessive daytime sleepiness. So, if it works in narcolepsy to treat excessive daytime sleepiness, it is going to work in everyone that has excessive daytime sleepiness. We just didn’t have the indication for it. Idiopathic hypersomnina, unexplained sleepiness throughout the day, that’s an indication that they’re pursuing right now…so yes, definitely to take a look and use it where it’s not a completely fluid narcoleptic patient. Yes, absolutely, we were told to broaden that scope outside the box.”

Q: “Is that essentially off-label prescribing that they’re suggesting?

A: “Yes, that’s definitely off-label for sure. 100%. Did we ever read that in writing? No, absolutely not. No. No one would put that in writing.” – Ex-Harmony territory manager for an eastern state
Ex-employees alleged collusion between territory managers and physicians to send in patient referral forms that were off-label or didn’t meet reimbursement criteria. As we shall detail, Harmony allegedly employs an unusual salesforce compensation plan as the key to its scheme – reps allegedly get paid for any patient referral forms faxed into the hub, even if they get rejected or the patient is never approved or goes on the drug. We presume this has the obvious and intended effect: reps proliferate bogus referral forms, particularly the top performers, according to ex-employees, with one stating a current territory manager “just [told] me yesterday that…he still does it”: “if you had a buddy, a doctor and say, hey listen, submit the form and then just ghost them...just submit the form and don’t even worry about...the insurance information...I’ll get paid for it...some representatives did that frequently.”

Reps allegedly colluding with doctors they’re close to to proliferate fake referral forms, per the alleged comp plan
A: “There were also some reps that, since we were paid only, pretty much only on driving those referrals in, if you had a buddy, a doctor and say, hey listen, submit the form and then just ghost them. Don’t even worry about it. Just submit the form and don’t even worry about filling out the insurance information. I'll get paid for it and then tell them that the patient changed their mind, or you changed their mind, or you went in another direction, or whatever. I guess that there are some representatives that did that frequently. Really, that was my motivation to see those refill links because I wanted to know how this one representative in Columbus, Ohio—my goal was 20, and she was putting up 50, 60 a quarter, every quarter. I'm like, I wonder how many of those patients are really on drug, and how many were just "fill out the form and don't worry about it." I know it goes on. I had a representative just yesterday tell me that, yeah, he still does it.”
Q: “Still does what? That he’s just submitting scripts he knows aren’t going to get approved?”
A: “Yeah. You have somebody who’s a good friend of yours—because you’re really asking a lot to do that. You’re asking a doctor to pretty much go against a lot of what he was trained upon. That's not appropriate. So, he better be even more than a guy you have beers with. He better be your buddy. And you can ask him and say, hey, just submit it, and I get credit and then forget about it. I know it goes on, but I don't know what degree. I suspect that some of the very successful reps quarter over quarter over quarter with no downturn because it's cyclic, it is, it's a rare disease, and it becomes cyclical, you're not going to hit your number every single quarter. You're certainly not going to blow your number out every quarter, and there are a handful of representatives at Harmony that continually do quarter over quarter. I suspect that was part of their plan, part of the process, but I don’t know that for a fact.” – Ex-Harmony territory manager for an eastern state

Source: Scorpion Capital consultation calls with experts
A number of ex-territory managers confirmed the widespread nature of the practice: “people on my team...would just go and find a doctor and hey man, just try to send as many through for me as you can...if they became close with the doc, then they could...send them through.” The conduct appears to be an open secret inside the company, with ex-employees conveying skepticism at highly unusual prescription volumes and patterns in various territories, where reps were “finding” far more narcolepsy patients than plausible: “you would wonder, how do you get all these through?”; “you would look at it and go, wait a minute, how does that happen?”; “oh my god, you would have one territory that had 40 [patients]...and ones that would have 5...and you’re going, those are the same sized cities...it’s like, wait a minute....”

Surprise and skepticism in salesforce of referral forms being jammed into the hub; huge anomalies across the company with prescriptions far higher than plausible number of narcolepsy patients; weird swings

A: “There were people on my team when they said they would just go and find a doctor and hey, man, just try to send as many through for me as you can...if they became close with the doc, then they could try to get them to send them through.”

Q: “And were the doctors playing along?

A: “I don't know. That's a good question. Good question. But you would wonder, how do you get all these through? It's like January; how are you getting all these through when this is a rare disease? And you would look at it and go, wait a minute, how does that happen?”

Q: “So, there were territories where you were saying they just had way more prescriptions than there could be narcolepsy patients? It sounds like that's what you're saying?”

A: “Oh my god, you would have a territory that had 40 and other ones that would have 5. And you look at it, and you're going, those are the same sized cities. How is that happening? It's like, wait a minute. For narcolepsy, you could take the population of Philadelphia and take the population of Washington, DC and say, here's how many there are per capita of narcolepsy patients. And it wouldn't add up when you look at the territories because how does one have that much more than the other on a consistent basis? I still scratched my head, going, what? And it's weird. you would look across the board, and you'd be like, how is it possible for that? How is the discrepancy possible to be from like 5 to 40 or 5 to 50 or something like that in a quarter, quarter by quarter?” – Ex-Harmony territory manager for a large Midwest state

Source: Scorpion Capital consultation calls with experts
Ex-employees described the lengths that territory managers allegedly go to “find” narcolepsy patients with EDS or cataplexy, stating that they “do all the specialty pharmacy work” for the doctor’s office; “they’ll sit there with the MA and find patients that they can, let’s go through your patients and find out what patients...are a candidate for Wakix...they’re still complaining of being sleepy...let’s get a list, call the patients in...I’ll help you fill out a form...” A former territory manager stated “no, honestly” when we asked if this is allowed, adding that “you’re really forced to do that...and you can stay and do it or...you can leave...they don’t want to know...don’t tell me...just don’t tell me.”

Reps allegedly engaging in aggressive, unethical practices to find off-label patients for EDS; pressure to do so to keep your job
Q: “What were some of those things outside the “boundaries of compliance” that Harmony is “forcing reps to do”?
A: “They go in, and they do all the specialty pharmacy work for them, they do all of the pharmacy for them in the office. They’ll fax them in. They’ll sit there with the MA and find patients that they can, let’s go through your patients and find out what patients are on modafinil and are they a candidate for Wakix. They’ve been on modafinil for five years. They’re still kind of complaining of being sleepy. Let’s try those. Let’s get a list, call the patients in, I’ll help you fill out a form, send them in—stuff like that.”
Q: “Is that not allowed?”
A: “No, honestly, in order to make goal in a lot of these companies and the way that they raise your commission, you’re really forced to do that. And you can stay and do it, or you cannot, and you can leave. If you’re not happy there and you’re not going to make goal, then you’ve got a couple of choices you can make. Did the managers know that reps are doing this? If they do, they’re blind to it, they don’t want to know. Don’t tell me. Just don’t tell me. Does upper management now? Probably not, or they do, and they just don’t want to admit it, think about it, or inquire about it.” – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
A high volume prescriber and speaker for Harmony confirmed the color from reps regarding alleged off-label prescribing, stating that “the speakers that you’re talking about…they’re doing to give it to excessive daytime sleepiness patients because you can find a lot of those, and it’s an unclear diagnosis, and you can put them on it.” A former territory manager provided an example of the unusual patient flows that would result, speaking sarcastically of a colleague: “I don’t know why there are 30 or 40 narcolepsy patients…in Flint, Michigan…no idea why…but she’s doing it, and she’s making a crap ton of money doing it.”

Harmony speakers are actively pushing the drug off-label for EDS in the absence of narcolepsy

“I think the speakers that you’re talking about, they’re going to give it to excessive daytime sleepiness patients because you can find a lot of those, and it’s an unclear diagnosis, and you can put them on it…”-Neurologist in New York with 70-80 narcolepsy patients

 Territory manager is skeptical of a rep with an unusually large number of narcolepsy patients in Flint, Michigan

“I think it would depend on the geography that you cover because there’s like one girl - she’s in Flint, Michigan, I believe - she does like 30 or 40 prescriptions in a quarter, which is amazing. I don’t know why there are 30 or 40 narcolepsy patients or so many narcolepsy patients in Flint, Michigan, no idea why. But she’s doing it, and she’s making a crap ton of money doing it.” – Ex-Harmony territory manager for several states in the Northeast
The key enabler of the alleged off-label scheme is a highly unusual comp plan that allegedly compensates territory managers exclusively or almost exclusively only on the number of patient referral forms faxed into Harmony’s hub - irrespective of whether they are on-label or comply with insurance requirements. In other words, reps are allegedly compensated even for enrollment forms where the patient is never approved or goes on the drug. Instead of writing a prescription on a pad, doctors or their staff fax a referral form to initiate the process of getting a patient onto Wakix. Every single former territory manager we interviewed conveyed that the plan was extremely unusual and that they have never seen anything similar. Common sense indicates that the only purpose of such a plan is to incentivize sales reps to proliferate inappropriate patient referral forms: “I’ve never seen a company in my life do that. Never. I’ve been in pharmaceuticals for 10 years…weird, right?...you look at that and – this is really weird, really odd.”

Comp plan based on faxed referrals was highly unusual and “really weird, really odd”
“You would have reps that you would hear - like some of the people that are maybe the top five people in the company - and you would hear stories as a rep, and *they're just going to that office, they just sent a bunch of stuff through*—I don't even care. Put it through the fax machine, and as soon as you hit send, I get credit for it. I've never seen a company in my life do that. Never. I've been in pharmaceuticals for 10 years, and I've been in other sales before that. I've never seen people just get credit as soon as it goes through the fax machine. Because normally, a company does not want to pay you until they get paid. *Weird, right? You look at that and—this is really weird, really odd.*” – Ex-Harmony territory manager for a large Midwest state

Paid on patient referrals/scripts
Q: “What did Harmony do in terms of your compensation? Were you compensated based on the number of cataplexy diagnoses you got?”
A: “No, *you're just compensated based on your scripts.*” – Ex-Harmony territory manager for a large region in the southeast across two states

Source: Scorpion Capital consultation calls with experts
An ex-territory manager described how the comp plan incentivizes and pressures reps to cross the line, and alleged that most are therefore not compliant: “that kind of pressure...it really put pressure on the salesforce because it incentivizes them to go outside those boundaries – and all of them do it...so ridiculous is how they’re forcing reps to work outside the boundaries of compliance...and all of them do it.” He stated that the plan is not based on “market demand” or “patient demographics,” similar to another ex-manager who indicated that Harmony sets quotas far in excess of the number of possible narcolepsy patients in a region: “it “makes no sense whatsoever...I don’t know what methodology they were using to figure that out...the numbers never matched up.”

Comp plan incentives and pressures reps to “work outside the boundaries of compliance”

Q: “Was there anything in the compensation plan or instructions you were given that didn’t sit right with you?
A: “I mean, it's always up to the salesperson to do what they want to do. They've got to pick their own path, and they've got to be ethical or not. The only thing that really pressures you and especially in the rare disease business, is they bring you in, and it's like, "Oh, you've got to get six scripts a quarter." That's it. I forgot what mine was. I got to get 10 scripts a year or something. They just raise the goal like crazy, like 25%, and you're like, what the heck? This is like specialty rare disease. We're not talking diabetes. And so, that kind of pressure, the way that they incentivize and change commission structure, it really put pressure on the salesforce because it incentivizes them to go outside those boundaries—and all of them do it...They base the quota on your history and what you've done in that territory versus basing it on market demand, basing it on patient demographics. There are only 200,000 patients a year. We can only get so many a year. And so that, to me, is what's so ridiculous is how they're forcing reps to work outside the boundaries of compliance when they do that. And all of them do it. I take that back. I shouldn't say all of them do it.” – Ex-Harmony territory manager for a large region in the southeast across two states

Company allegedly sets quotas far in excess of probably narcolepsy patients in a territory;
“You have to remember, it’s rare disease. So, the number that Harmony upper management is putting out like even in my territory, which was [state redacted], the amount of prescriptions that I had to get in a quarter was more than the rep in Manhattan had, which actually makes no sense whatsoever. But I don't know what methodology they were using to figure that out. While my geography may have been bigger, obviously, there are more people and potential for a patient in a geography like Manhattan because there are just more people there. The numbers never matched up to me. I did very well while I was there. I've always been a top performer. I was at [large pharma company] for [number redacted] years, always a top performer there. I left there at the top of my game.” – Ex-Harmony territory manager for several states in the Northeast

Source: Scorpion Capital consultation calls with experts
Territory managers emphasized how aberrant the comp plan is – “different than any place that I’ve ever worked in my career…it’s kind of weird.” One explained that the second a prescription goes across a fax machine at the hub, the rep gets credit for it: “so, if you had an office that just faxed five in for you and none of them got filled, that sales rep gets credit for it, even though none of those five got filled. There could have been no chance in hell that those are getting filled, but the rep just got credit for it just because it went through the fax machine, even though those never shipped. So, the whole process is weird.”

“ Weird” comp plan based on faxes into the hub even if scrip never gets filled; reps indicate they have never seen that kind of comp plan before; rep gets paid “even if no chance in hell that hose are getting filled” or shipped to a patient
A: “You don’t get credit for the refills. You don’t really see that number.”
Q: “So, what did you make of that?”
A: “That’s a little weird. The whole sales process there is a little weird because you get credit when the fax goes through the fax machine. Have you been told that before?
Q: “No.”
A: “So, you get credit—this is different than any place that I’ve ever worked in my career. And if you ask somebody at Harmony, it sounded like from talking with everybody that, again, it’s kind of weird. So, if you put a fax through the fax machine, and it goes over, and it goes to this hub, and there are three different hubs that they can go to. First of all, it goes to Harmony’s hub. Harmony takes that prescription, they’ll look at it, and they say okay, now where do we go to get the script covered? Then Harmony would scrub that prescription, which came in via the fax, and they would take it and send it to whatever specialty pharmacy of those three that they thought had the best chance of covering that medication and to get it for that office and the patient. Once that prescription goes through the fax machine, the rep gets credit for the script. Normally the way that it works is the rep doesn’t get credit for the script until it ships out to the patient, meaning now that medication can be charged and the insurance company has to pay for the medication because it’s been shipped. So now, I’m giving credit to the rep because it’s been shipped. That isn’t how they do it. They give credit when it goes into that specialty hub. That was a little weird. And so, if you had an office that just faxed five in for you and none of them got filled, that sales rep gets credit for it, even though none of those five got filled. There could have been no chance in hell that those are getting filled, but the rep just got credit for it just because it went through the fax machine, even though those never shipped. So, the whole process is weird.” – Ex-Harmony territory manager for a large Midwest state

Source: Scorpion Capital consultation calls with experts
Another ex-territory manager stated that the comp plan “deviates from anything I’ve seen in specialty pharma” and explained the perverse incentive it creates to get patients on drug even if they’re not on label, with no incentive to keep them on it: “the sales consultant have no skin in the game to keep a patient on drug, and, even more importantly, no sales consultant has any transparency or visibility into how many patients are on drug in their territory. I have never seen that before in a pharma company.”

“Overwhelming” internal sense at Harmony that they’re “fudging the numbers” re new patients starts and discontinuation rate; compensation structure “deviates from anything I’ve seen in specialty pharma”; reps have no visibility into number of patients on drug in their territory – “never seen that before in a pharma company” – no any incentive to keep them on

A: “The overwhelming sense in the company is they are fudging the numbers. I couldn't really get a sense whether that - basically, they're clouding, obfuscating, fudging the numbers around two things: how many patients are on drug at any one time and what is the discontinuation rate. Nobody that I talked to is privy to those numbers. What I thought was really interesting because it deviates from anything I've seen in specialty pharma - the compensation structure to the sales consultant is as follows: every quarter, the number of patients—let's average it at 15 new patients per quarter, so brand-new, novice patients to the drug. They have to get 15 forms faxed in for benefit verification to initiate therapy.”

Q: “So, you’re saying you get the form faxed in. So, you get the doctor to write the script.”
A: “Yup. So, 70% is just getting the form sent in. I don't know if this is true, but I think maybe it may come on their earnings calls, they are referencing the number of patients that have formed new starts that were faxed in. So, they're using that as a bellwether for a proxy for success. In the compensation structure, there is no component of the bonus tied to overall volume. So, the sales consultant have no skin in the game to keep a patient on drug, and, even more importantly, no sales consultant has any transparency or visibility into how many patients are on drug in their territory. I have never seen that before in a pharma company.” – Ex-Harmony territory manager for a large region in the northeast

Source: Scorpion Capital consultation calls with experts
One of the most troubling features of the comp plan is that reps allegedly are kept in the dark about the number of patients on drug in their territory. An ex-territory manager stated “it is so hidden – they’re going to enormous lengths…they’re blinding their sales consultants to patients…they’re investing no energy in the patient staying on the drug…none…that’s not a long term play.”

Harmony going to “enormous lengths” to prevent reps form knowing number of patients; “focused solely on just new starts and hiding all data from everybody”; “not a long term play”; internal “sentiment was it’s all bullshit and they’re trying to hide it”; all about number of forms faxed into the hub

Q: “They don’t want them to know the discontinuation rates?”
A: “Yeah, so imagine that the rep goes out, and the only thing they see is new starts for that quarter and if the patient went on drug. Now, it’s such a tiny window, and it is so hidden - they’re going to enormous lengths in my mind. And maybe I’m wrong, and maybe there are other companies that do this; I’d never seen it. They’re blinding their sales consultants to patients - basically, they’re investing no energy in the patient staying on drug. None. That’s not a long-term play, it’s just not because any sustainable pharma company knows that it’s as easy to keep a patient on drug as to get a new patient, but these guys seem to be just—not seem—they are focused solely on just new starts and hiding all data from everybody.”

Q: “And how did your contacts interpret that? Is it that they don’t want the salesforce to get demoralized because most of their patients are dropping off? Or they want to be able to promote a number to Wall Street that, internally, people would say it was kind of nonsense?”
A: “The person I spoke to specifically gave me these details. Certainly, his sentiment was it’s all bullshit, and they’re trying to hide it in terms of, essentially, they don’t want anybody seeing or having access or eyes on discontinuation rates and/or patients on drug. There’s no other way to interpret that…The big takeaway is that the salesforce is not incentivized in any shape or form to keep patients on drug, to sustain volume. It is purely a new patient machine, how many forms you’re getting across the finish line—how many forms are you getting into the hub and how many are going on drug? It’s all very short-term.” – Ex-Harmony territory manager for a large region in the northeast

Source: Scorpion Capital consultation calls with experts
The “enormous lengths” that Harmony goes to to keep sales rep in the dark once the prescription is faxed to the hub was a recurring theme of our interviews, suggesting questionable behavior at the next step of the process flow, which involved reimbursement and Harmony’s three key specialty pharmacies. Territory managers stated the forms were always faxed to one machine, emphasizing how irregular it was to have a centralized fax machine: “it’s all manual, as much as the salesforce fought to get everything digitized”; “all of the prescriptions went to a fax machine at RareMed…I don’t know how that happens on that end…that’s above my pay grade…they would communicate that information to [name redacted], the director of patient services.” Another former rep stated that “once the referral went in, we were out of the picture…we couldn’t support anything.”

**Manual process where “special form” went to a fax machine at a centralized hub; salesforce pushed to have it digitized**

“It's not like a typical prescription process where if you go to your doctor and you need an antibiotic, he writes it, you go and pick it up at the pharmacy. **You have to fill out a special form, and it’s all manual, as much as the salesforce fought to get everything digitalized**, especially in this world that we’re living in post-covid. They just have not done it. But there's a form that has to be filled out manually. It includes all the patient information. It includes the patient insurance information and then includes the office and doctor information. The patient has to sign the form. They don't have to sign it while they’re, just in case they forget; once it goes to the centralized hub, they will contact the patient to get the signature if the office did not…They contracted that out to RareMed, and so all of the prescriptions went to a fax machine at RareMed, and then RareMed communicated the information—I don’t know how that happens on that end; that’s above my pay grade—and then they would communicate that information to [name redacted], the director of patient services.” – Ex-Harmony territory manager for several states in the northeast

**Reps “out of the picture” one referrals went in**

“Once the referral went in, we were out of the picture. We couldn’t support anything.. ” – Ex-Harmony territory manager for a large region in the southeast

**Enrollment forms used, not prescriptions**

“Doctors had to fill it out - **it wasn’t like a prescription that they would write on a prescription pad**. They would actually have to fill out this enrollment form, which Harmony called a referral form and fax that into our hub, and then our hub would triage the prescription over to one of the specialty pharmacies. Our hub was a nightmare. – Ex-Harmony territory manager for a large region in the northeast, covering three states

Source: Scorpion Capital consultation calls with experts
We suspect that given the unusual compensation scheme and alleged number of off-label or other non-compliant prescriptions, Harmony is keen to avoid a paper trail and seeks to limit the submitted forms to an inner circle. A former territory manager stated that “all of the other companies that I’ve worked for were all EMR…you went through electronic medical records…this thing is like a fax, a piece of paper, which was really odd that it didn’t go through a computer.” The rep added that the field pushed for electronic submissions but Harmony refused: “saying no, we want everything to go through a fax machine…was a little odd to me…and I asked that question to a lot of people, and nobody could ever explain that to me.” The rep noted that a fax may not even compliant, saying you can get fined in certain states if not on EMR and can lose Medicare/Medicaid business if not using one.

Reps thought it was unusual for force referrals into a fax machine vs. EMR as is standard practice; reps pushed for EME but “nobody could explain that to me ever”; Harmony allegedly forced this even though could get fined without EMR

A: “Why do you think they were on a fax form? All of the other companies that I’ve worked for were all EMR. You went through electronic medical records. This thing is like a fax, la piece of paper, which was really odd that it didn’t go through a computer.”

Q: “Yeah, that is really weird.”

A: “All companies now have offices with EMR things in them. Every office is set up on an EMR system. In the state of [redacted], if you’re not on an EMR system, you get fined. You lose a portion of Medicare/Medicaid business because you’re not using EMR, so they incentivize everybody to use it, and all the offices have electronic medical records, and they all carry laptops around, and you hit a button, and you send that information over to the specialty pharmacy or wherever you’re going, whatever hub that you’re working through, and it’s easy. Why they were operating like they were from 1980 or 1990 and saying no, we want everything to go through a fax machine, not electronically through a computer, was a little odd to me. And I asked that question to a lot of people, and nobody could ever explain that to me.” – Ex-Harmony territory manager for a large Midwest state

Source: Scorpion Capital consultation calls with experts
Ex-employees indicated that territory managers were completely shut out once a prescription was faxed in: “that was by design that the salesforce was…purposefully kept in the dark…it was a weird situation”; “we had no idea…they completely boxed us out, which is very atypical within the rare disease business…it doesn’t happen…you don’t know what’s going on…you have no clue…they won’t tell you…there’s nobody I can call at corporate…I have to just keep my mouth shut…I don’t know the reason behind it.”

**Territory managers “completely boxed out” of any info about paperwork like prescriptions, enrollment forms, supporting documentation**

“There was always paperwork that had to be sent in, in addition to the enrollment form, and that's the biggie. Then you've got to have supporting documentation, and so that documentation gets faxed in…they wouldn't let us know in the salesforce; we had no idea. They completely boxed us out, which is very atypical within the rare disease biosciences, but especially in rare disease, it doesn't happen. The reps, there are no HIPAA violations, but you are aware of the situation…they just completely boxed everybody out, and you have days and weeks go on where, as a rep, you don’t know what’s going on. You have no clue, they won't tell you…there's nobody I can call at corporate to facilitate it, and so, I have to just keep my mouth shut…I don’t know the reason behind it.” – Ex-Harmony territory manager for a large region in the southeast

**Sales was “purposefully kept in the blind”; “by design”; “a weird situation”**

“That was by design that the salesforce was really, I think, purposefully kept in the blind. I don't know. It was a weird situation. There wasn’t a lot of communication between corporate and the salesforce.” – Ex-Harmony territory manager for a large region in the southeast

Source: Scorpion Capital consultation calls with experts
One of our best sources was a former field reimbursement manager who worked with a large number of territory managers – over 15, giving him wide visibility - as well as the regional managers they reported to. We interviewed him twice over several hours, given the depth of his knowledge into Harmony’s practices and his long background in big pharma reimbursement. The following pages detail the detailed and damning color he provided. He began by estimating that more than 40% of prescriptions were off-label and stated that the entire strategy was to push for off-label sleepiness in the absence of cataplexy; to misrepresent other drugs patients had to fail first; and that reps were incentivized to engage in the conduct.

Allegedly more than 40% of scripts were off-label; strategy was to push for off-label sleepiness in the absence of cataplexy, and to misrepresent other drugs they had to fail first; regional managers and reps were incentivized for this behavior.

Q: “How many off-label scripts were being written?”
A: “Depending upon the regional manager— I would have every reason to believe that [redacted] would encourage—because [redacted’s] compensated on those, too, right? [Redacted] is compensated on the performance of the sales reps, so [redacted] makes more money on the number of referrals, indicated, not indicated, just like the sales rep does.”

Q: “What percentage of the scripts that were coming through were off-label?”
A: “I would say 40% and above.”
Q: “And what were some of the off-label indications they were putting on there?”
A: “A lot of it was excessive sleepiness. And then they would also exaggerate on different generics that they had failed because you have to fail generics for a certain period of time. Keep in mind, Wakix is one of those add-on drugs; it's a "me too" drug. So, you don't specifically yank them off of the generic stimulant. You add Wakix to it. That's the strategy.”

Q: “The label says it's indicated for excessive daytime sleepiness. How is that off-label, then?”
A: “Nope. There are two indications: It was cataplexy and narcolepsy. Now, cataplexy, in my opinion, is probably ultra-rare. I mean, it's ultra-rare. Narcolepsy's rare, and cataplexy's ultra-rare.”

Q: “I see. So, it says, "narcolepsy plus EDS or narcolepsy plus cataplexy." So, you're saying they're prescribing to patients that don't have narcolepsy. It's not just for sleepiness.”
A: “Yup. Oh, no, no, no, not at all.”

Q: “So, you're saying they were just prescribing it for people with sleepiness? Okay. If there's a lot of that off-label usage, was that essentially being promoted by the company to doctors through a wink-wink because that's the only way that everybody can get more scripts and all these people in the speaker's program?”
A: “[chuckles, then laughs] You've been doing your homework, haven't you, sir?” -Ex-field reimbursement manager working with Harmony
He stated that as a result of the comp plan, “reps were getting paid on the referrals if it was on-label or not” – that all they had to do was get a doctor to “fill out the form and fax it into the reimbursement hub…that’s it…that’s what they get paid on.” He indicated it was highly prevalent and brought to the attention of “senior leadership” on numerous occasions: “People aren’t stupid…the more successful sales reps were taking advantage of that…we had pointed it out to our senior leadership and their leadership…I mean, it doesn’t take a whole lot to figure that out.” His comments were striking in describing it as an open secret: “[I couldn’t count how many of those referrals were off-label excessive sleepiness. I couldn’t count them. And everyone knew. Everyone knew that.”

Comp plan paid reps for off-label referral forms; highly prevalent practice across the salesforce; open secret in the company; was brought to “senior leadership” attention on numerous occasions

Q: “I talked to former sales reps, and they're like, nobody knew the patients on drug. You get compensated on new scrips. You’d ask your regional manager, how many of the patients are still on drug and nobody knew. It's weird they don't want people to know.”

A: “I think that's part of it. Another part of it was that they got paid on referrals. A referral is whenever a provider or a provider's office fills out the form and faxes it into the reimbursement hub. That's it. That's what they get paid on. It could be off-label. It could be—it doesn't really matter if it was adjudicated or not. They get paid on that piece of paper. And that was an issue that I had in the very beginning because it just makes everyone's life more complicated whenever you have a sales rep that might be misrepresenting what the drug could be used for simply because they were getting paid on those referrals, not on the fulfillment of the drug itself.”

Q: “A lot. How often do you think that would happen? People aren't stupid. I can tell you the more successful sales reps were taking advantage of that. And we had pointed it out to our senior leadership and their leadership on numerous—I mean, it doesn't take a whole lot to figure that out.”

A: “Yeah, there are criteria for those two disease states that Wakix has. And you can manipulate those criteria a little bit… I mean, excessive sleepiness is not an indication for Wakix, and I couldn’t count how many of those referrals were excessive sleepiness. I couldn’t count them. And everyone knew. Everyone knew that.”

Q: “They were just writing scripts for excessive sleepiness off-label - anyone has excessive sleepiness if they feel sleepy that day?

A: “They were getting paid on the referrals if it was on-label or not.”
He explained how he and other field reimbursement managers working with Harmony came to realize the mechanics of the off-label scheme, whereby reps would proliferate prescriptions and then hound field reimbursement staff for the information the doctor indicated on the prescription form – which they then used to magically convert off-label prescriptions to “on-label.” He stated that reps badgered him and other reimbursement staff for this info “oh holy sheep shit, all the time,” adding that if the rep was denied the info that “then the management would” get it for them.

Managers and reps allegedly trying to game off-label scrips “all the time”

Q: “How often were sales reps asking you for the indication and whether it was off-label?”
A: “Oh, holy sheep shit, all the time. All the time because that's low-hanging fruit.”
Q: “Every sales rep was asking you what the indication was and if it was off-label or not or rejected for being off-label?”
A: “Sure. "[redacted], do you know what they put down?" "No." "Well, I really need to know. I need to know if I can go in and re-educate the office on what the indications are." "Well, it wasn't what was necessary." "But what is it?" And so they would use that alibi that they can go in and say, hey, you know what?... . If they ask, and if I can get the data and provide it to them, I will. Because everyone wants their teammates to be successful.”

Q: “So, you're saying that reps would pretty much always get the question answered?”
A: “I would say yes. I mean, one way or another, yes. And if they didn't get the answer, then the management would.”
Q: “And they were getting it from your team or the hub, or where are they getting it?”
A: “Both. It's not illegal. I don't think it's illegal for me to provide—I don't think that's HIPAA data because there's no name associated. It's just an indication. It's like one of these 20 was this, and then they would go in and fish.” -Ex-field reimbursement manager working with Harmony
He described the “wow” moment when he and others figured out how reps were pushing off-label prescriptions: “there was really nothing to stop it…there was pressure from management to deliver…the pressure is there.” He painted reimbursement staff as fighting a losing battle in the face of aggressive sales managers who didn’t want to hear that “that’s not an indication supported for this drug” – “Can you possibly stretch? Can you possibly make excessive sleepiness narcolepsy? Can you possibly make it cataplexy? Can you possibly do that?"

Reimbursement staff eventually figured out the company strategy behind the alleged fraud

Q: “So, they were basically asking for information in a way that technically might not violate the law but would help them figure out—”
A: “The idea is they could potentially go in and re-educate the office on re-evaluating the signs and symptoms. Honestly, I could never wrap my head around why and then one of my peers said, "Dumbass, this is why. Don't you think they're doing that?" And it's like, "Oh my gosh." And then you start looking at the trend of the referrals that are getting approved compared to the ones that were not getting approved, and you're like, "Wow."

Q: “It sounds like the entire compensation scheme was designed to promote off-label prescribing.”
A: “I don't know if that would be a scheme, but there was really nothing there to stop it. I mean, whenever I was with [company name redacted], they were just black-and-white things that kept the communications with the sales reps on the commercial team; it was black and white. We just didn't do it. You would never provide—that information would never be provided, or it couldn't be provided, and it shouldn't even be asked. But not at Harmony. And the sales directors, they get paid on those just like the sales reps, no matter what it is…I think that there was pressure from management to deliver…the pressure is there.” -Ex-field reimbursement manager working with Harmony

Reps were using information on referral forms to push through off-label prescriptions by faking the indication

Q: “You'd observe them sending in these bullshit referrals. What would you do? Would they get some of those through the system? Were you getting pressure from Harmony? Harmony's incentive is the same as the rep, right?”
A: “There were a number of times when it was off-label, and whenever we provided that insight, for example, the sales reps would realize I've got so many referrals. These referrals came in. So, they would come to me and say, "What happened to these referrals?" Okay, "Dr. [redacted] gave me four referrals last month and five referrals before that. Whatever happened to those?" Well, in this particular case, at least two referrals out of five were off-label. "What do you mean they're off-label?" "They were off-label, excessive sleepiness. That's not an indication supported for this drug." Now, what does the sales rep do with that information? Did they go back in and say, "Can you possibly stretch? Can you possibly make excessive sleepiness narcolepsy? Can you possibly make it cataplexy? Can you possibly do that?" Now, did they do that with that information of the insights I was giving to them? I don’t know. But they certainly have the incentive to do that.” – Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
He expressed incredulity at the highly anomalous number of Wakix prescriptions for such a rare disease, allegedly facilitated by management who he stated hired regional managers to implement an off-label playbook: “I have dealt with other rare diseases…I mean, I just wasn’t accustomed to those kinds of numbers.” He provided an example of an underperforming territory where a new regional manager did “whatever it takes” to “all of a sudden” create an explosion in prescriptions: “I’ve been in the pharmaceutical industry my entire career. And you see stuff like this. You see it. It rarely lasts.”

Highly anomalous number of scrips for such a rare disease; allegedly facilitated by management who brought in regional managers with an off-label playbook that magically led to an explosion of scrips; “whatever it takes”
A: “...I have dealt with other rare diseases. I mean, I just wasn't accustomed to those kinds of numbers.”
Q: “Was there anything that you ever heard from leadership or from any of these reps or people like [redacted] said that where leadership was encouraging them to do this?”
A: “In fact, that was one of the reasons why [redacted] was brought in is because the numbers were not being met.”
Q: “And did they know [redacted’s] modus operandi?”
A: “I mean, listen…I've been in the pharmaceutical—I mean, I'm [redacted age]. I've been in the pharmaceutical industry my entire career. And you see stuff like this. You see it. It rarely lasts. I mean, a person like that rarely lasts, but you see it. Same people—well, I shouldn't say the same people because a lot of those individuals left, and they were replaced by someone else. But same providers, same metropolitan areas, same indications, right?”
Q: “And then you're saying a new territory manager comes up, and all of a sudden, their prescriptions explode? Is that the point you're making?”
A: “Yes, sir. All of a sudden, right, especially whenever the person, whenever [redacted] is hired, tells the team, we will be number one. We will take this territory, [region redacted]—and we will be the number one territory in the United States. And [redacted] is like, "I'll make sure of it." Now, it’s that a rah-rah session? Is that inspiring? Or is it kind of like, whatever it takes?” -Ex-field reimbursement manager working with Harmony.
The ex-field reimbursement manager stated that the number of narcolepsy patients Wakix sales managers and their doctors are finding is simply implausible, speaking facetiously: “I was stunned at how many cataplexy and narcolepsy patients that are legitimately out there. I was stunned. Stunned…I was just amazed…that every month that these different providers have…identified so many patients…we’re not talking about an autoimmune disease…it’s almost like narcolepsy’s a pandemic, not a rare disease.”

Reimbursement manager expressed incredulity at the implausible numbers of narcolepsy patients being prescribed vs. the actual prevalence of such a rare disease

Q: “You had chuckled earlier when you said, oh, you understand how this stuff works when I’d asked if the company was pushing this whole off-label prescribing stuff because it’s the only way you can show growth. There are just not enough narcolepsy patients out there. What were you chuckling at? What did you observe that made you think that?”
A: “I was stunned at how many cataplexy and narcolepsy patients that are legitimately out there. I was stunned. Stunned. I mean, they’re not just going to a sleep specialist, they’re actually going to DOs, and they’re going to MDs, I mean, regular practitioners. I was just amazed, just amazed how many patients that were out there that legitimately or not actually had this disease.”

Q: “Are you kind of being sarcastic here? Or are you making a statement of fact, like you were just shocked that there were this many narcolepsy patients because it's such a rare disease, or you were just genuinely surprised that there were that many, and it was an aha moment? I couldn't make out what you were implying there.”
A: “No, no, no. I was just surprised, kind of surprised, that every month that these different providers have, or they’ve identified so many patients. I mean, honestly. Again, we’re not talking about an autoimmune disease.”

Q: “It sounds like you’re being cynically surprised at the number of patients. Am I interpreting you correctly?”
A: “Yeah, I mean, consistently. Week after week, month after month, yes…It’s almost like narcolepsy’s a pandemic, not a rare disease.” -Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
He highlighted the aberrant nature of the incentive plan – “this is the only situation I’m aware of in my tenure working in reimbursement” and wondered why the rep is getting paid “for patients that don’t get the drug...no one else is getting paid.” Then he explained why: reps were incentivized to proliferate off-label prescriptions as they could then “go back in and salvage two or three of those patients that were off-label – but my question is, what happened to make from off-label to on-label?...I mean, did the patient suddenly get worse?”

Compensation structure was allegedly designed to incentivize off-label fraud; regional managers and reps hounded reimbursement staff for information they could use to convert off-label scrips to on-label

Q: “What's your commentary on what you think is essentially fraudulent, because that's basically what you're describing. And, by the way, you're not the only person to describe that to me.”
A: “I would say whenever you're compensating someone—this is the only situation that I'm aware of in my tenure working in reimbursement, working in contract management, working with Cigna's and the Aetna's and even working with the smaller Blues plans and the Medicaid plans...I'm trying to give kind of a global perspective on how one makes this assessment. I mean, you don't get paid for patients that don't get the drug. You just don't. No one else is getting paid on that. The pharmacy is not getting paid.”

Q: “So, why do they do that? Because they just think they'll get a certain percentage of those through?”
A: “I think that's part of it. Part of the strategy might be that they can go back in and salvage. I mean, people go back in and salvage two or three of those patients that were off-label, hey—but my question is, what happened to make it from off-label to on-label? What happened? I mean, did the patient suddenly get worse?”

Q: “What were you observing over and over that led you to think that this was happening? I mean, obviously, I think you've talked about it, but just to make sure that I understood properly.”
A: “You know, why do you need to know that these were off-label? Why is that so important? Why do you need to know what the indication was that was originally given? I mean, it was off-label? I mean, maybe it was a hang-nail.” -Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
He stated that he interacted regularly with 17 Harmony territory managers, giving him wide visibility into Harmony’s business practices, and that a significant percentage were essentially faking prescriptions forms and still getting paid for it—“It was a huge red flag...quite a lot of these prescriptions were junk...they were just bullshit...I mean, they were for the wrong indication...not even narcolepsy, not even cataplexy...they were like for sleeping disorders – a sleeping disorder is not narcolepsy, ok?.” He indicated that the practice was so brazen that the prescriptions didn’t “even meet the most basic criteria for an indication....”

Sales reps were allegedly paid for “junk” prescriptions that had nothing to do with the label

Q: “But you or the person above you were essentially interacting with 17 sales reps or territory managers for Harmony?
A: “Yeah. I specifically was interacting with 17. The other field reimbursement managers had their territories, too. I mean, I managed [redacted number of] states.”

Q: “So, a pretty big swath of the country...what did you observe as far as red flags?
A: “That's a great question. The one thing that I noticed, it was a huge red flag - I mean, it just didn’t make sense that the salespeople were reimbursed on referrals or prescriptions. Quite a lot of these prescriptions were junk. They were just bullshit. I mean, they were for the wrong indication, you know, not even narcolepsy, not even cataplexy. They were like for sleeping disorders—a sleeping disorder is not narcolepsy, okay? So, you had reps getting paid fairly generously for offices providing a referral that didn’t even meet the indication, any of the indications, not even close.”

Q: “Was this that the rep was essentially kind of faking the indication, or the doctor was faking? What were they doing?
A: “The rep was taking advantage of the compensation strategy. I mean, there were two, and they specifically realized, in fact, I would chastise them.”

Q: “Was it that the doctors were - the rep says, oh, Dr. Such-and-such, okay, the patient doesn’t have cataplexy, but the patient looks pretty sleepy, whatever, just write them a script, maybe it'll help, and the doc says yes. Is that what was essentially going on that the doctor in conjunction with a rep, whether due to ignorance or the rep just trying to get their bonus, that that's essentially the game they were playing in the field?”
A: “I would say, in all transparency, that there were several of those reps that were probably doing just—not all of them. I can’t say that all [number redacted] of my sales professionals were doing that, but there were several that had to have, just had to have been providing half-truths, had to have been. I mean, why would you have your staff literally take 15-20 minutes and complete a referral form whenever there’s no indication—it doesn’t even meet the most basic criteria for the indication? Why would you do that? It’s a waste of time.” – Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
He opined that the off-label scheme was “a strategy that the company might have had from the very, very beginning” – “to be creative with the signs and symptoms so it would meet” narcolepsy or cataplexy. He explained in detail how reps pressured reimbursement staff to help them facilitate the fraud.

Regional managers and reps badgered reimbursement staff for rejection information to magically convert off-label scripts to “on-label” through “creative” diagnosing and coaching physicians and support staff; allegedly a company “strategy”

Q: “All the off-label stuff - wouldn't that get shut down by the insurers? How is it getting through? Where's the weak link in the chain?”
A: “Going back to the criteria, this is something that [redacted] would push, and [redacted] would want to know, so there are 10 referrals from this doctor. Why are only 5 of these being filled? Well, we had access to that data; they did not. So, they would push me. Well, [redacted], why are only half of these--? Well, because they were off-label? Well, what indications did they put down? Honestly, that's really none of your business what indication. But [redacted] would push for it. I think [redacted] would take that feedback from us, and take that to the rep and then the rep would go in and say, Hey, you remember those 10 referrals you said you put through? Well, only 5 of these were on-label. How can we creatively take a look at those 5 that were off-label, and could they possibly be narcolepsy instead of excessive daytime sleepiness? Could we possibly say that it's this by taking the patient information in such a way--? In my opinion, that was kind of a strategy that the company might have had from the very, very beginning.”

Q: “And so, who is having that conversation about, hey, can we be creative with the diagnosis? Is that the rep having that conversation with the doctor? Who's having that conversation?”
A: “It could be management. It could be the rep. But that question was always asked, and that was unusual. I mean, the question was always asked, well, why only half? Well, because it's off-label. Oh, well, what were they saying it was? But that's ammunition that [redacted] or the rep themselves could actually go in and say, I mean, [redacted] would say that they just go in and say, well, why is that? Are you sure it's only excessive sleepiness?”

Q: “So, they obviously are successful in getting these through these specialty pharmacies and not getting a rejection. Would you see a bunch of scripts rejected by a prescriber, and then all of a sudden, they’re not rejected because they successfully said the right thing? Did you observe that?”
A: “I could say, yeah. There was always an improvement...honestly, if someone could coach the individuals completing these referral forms on how to be successful with it and how to be creative with it, that would have an immediate impact if it was getting through the payors. The payors would tell you, no, we're not going to approve it because of this piece of criteria that we require is not there. Well, I didn't mention this, then. Oh, I didn't tell you this. Or, I've revised office notes. To answer your question, yes, I've seen offices be progressively more successful in getting Wakix prescribed...you could coach the doctors to say, well, it's not just the doctor. The doctor is not filling out the referral forms normally. You have support staff that does that. The doctor normally does not. So, the doctor should be educated on what those indications are, not how to be creative with the signs and symptoms so it would meet narcolepsy or it would meet cataplexy. But I see that happen. I mean, there were certain reps, and [redacted] was very good at that.” -Ex-field reimbursement manager working with Harmony
In addition to off-label abuses, he detailed the speaker’s program as a kickback scheme. He alleged that numerous sales reps that he interacted with left Harmony due to their concern – with many voicing their alarm to him personally - and shared examples of regional managers allegedly using the speakers program as a carrot as well as a stick. He stated that speaker who didn’t write enough prescriptions were threatened that “no, you can’t be a speaker for us because you don’t write enough” - or induced with “now, of you write more our drug, I’ll possibly look at making you a speaker.” He added that “you can’t do that…that’s the Stark law.”

Regional managers were allegedly threatening doctors on the speakers program if they didn’t write enough prescriptions: well-known practice in certain regions, resulting in sales reps leaving the company

A: “I’ll be very candid with you. I had sales reps that left Harmony, and they would tell me that their sales manager would be, "No, you can’t be a speaker for us because you don’t write enough. Now, if you write more of our drug, I’ll possibly look at making you a speaker." And you can’t do that. That’s the Stark law. There are federal statutes out there to stop that from happening.”

Q: “So, you heard this from sales reps? Sales reps were saying that their manager told the doctor that they’ll only get on the speaker’s program if they write more scripts?”

A: “Yup. Or the exact polar opposite. "You know, you’re currently a speaker with us, but you haven’t been writing as much as you used to. You know what? You may not be a speaker for us much longer if we don’t see these scripts go up because we need our speakers to have a lot more experience with Wakix." Now, you can’t do that. You just can’t do that. Did I hear sales managers say that? No. But I’ve had three sales reps say that about the sales, the same identical sales manager.”

Q: “Are you able to say which region that person was in?”

A: [geographic region redacted]

Q: “The [geographic region redacted] manager. How many sales managers like that were you interacting with? Was that the only one? Like one bad apple. Or were there a bunch of people like that?”

A: “I know that if it was one salesperson telling me this, that would be a different story. But whenever, you know, a third of the people are coming out and saying, “I can’t believe what this sales manager just said to my provider that I’ve been calling on now for three years. I mean, literally threatened them not being a speaker anymore if they didn’t pick up the volume.” And I’m just like, "Dude, they can’t say that." "Well, they did." – Ex-field reimbursement manager working with Harmony
He characterized the speaker’s program as a “leverage tool” over doctors, and stated that the practice was so prevalent that in his region it led to “half of the sales team bring[ing] it to [redacted’s] attention.” He stated in contrast to Harmony, a “compliance issue like that normally is taken very, very seriously.” He emphasized the concerns among the field that led to resignations: “there were other reps that left because of…there were other people that just didn’t like the pressure.”

Speakers program was used as a “leverage tool” over doctors
A: “We discussed this last time, too. [Redacted] would - there were numerous occasions whenever [redacted] would be in front of a provider and just say, you know, we may have to take you off this lucrative speaker’s program because you’re just not writing enough. You don't have enough clinical experience with our drug because you're not writing enough of it. Some doctors would take that offensively. And keep in mind, you know, Stark law; you can't do that. You can't provide compensation for speaking based upon—you can't use that as a leverage tool.”
Q: “You were there, and you heard this? Or you heard about it?
A: “Whenever half of the sales team brings that to [redacted’s] attention, I mean, we’re talking about a sales team of 8 or 10, and half of them are saying that [redacted] is doing that…I've worked for probably some of the larger biotech and pharmaceutical companies out there, and a compliance issue like that normally is taken very, very seriously. Very seriously. That's not something that you do. Doctors are not ignorant. They realize whenever something is—whenever a law is being broken, something like that because I assure you, they don't hear that comment from every pharmaceutical company that comes in and talks to them.”– Ex-field reimbursement manager working with Harmony

Sales reps left because of alleged pressure to push off-label scrips; given small number of narcolepsy patients, couldn’t hit quota without being “a little creative”
“…there were other reps that left because of—there were other people that just didn't like the pressure. We're not talking about rheumatoid arthritis. We're not talking about plaque psoriasis. We're not talking about migraines. There just is not a ton of patients that legitimately have narcolepsy and legitimately have cataplexy; there just aren’t. It’s a rare disease. Maybe the way they’re looking at it, in order for these numbers to be there, you’ve got to be a little creative.”-Ex-field reimbursement manager working with Harmony
He alleged that one of the sales managers known to be particularly aggressive in exploiting the speaker’s program is still employed by Harmony, despite the conduct being openly known. He told us that the pressure to assist these practices led to the majority of the field reimbursement team resigning, with perhaps “three of the original field reimbursement managers there…out of fifteen.”

High turnover among field reimbursement staff allegedly due to speaker program abuse and pressure to enable off-label prescriptions

Q: “Is this sales manager still there?”
A: “Oh, I’m sure [redacted] still is. I’m confident [redacted] still is. I mean, [redacted] was trying to make a big name for [redacted] in a very, very short period of time…my territory was constantly in flux because there was a pretty high turnover rate in reimbursement managers because these regional sales directors, like [redacted], were constantly beating up those reimbursement managers.”

Q: “So, you said this person was just badgering you to do this stuff? What was [redacted] trying to pressure you to do? You said that was one of the reasons that you left?”
A: “Well, it wasn’t just me. I think there might be three of the original field reimbursement managers there.”

Q: “Out of how many?”
A: “Out of 15.”

Q: “And they left because of what?”
A: “For the same reason, just the pressure from—the salespeople would understand.”

Q: “You’re being pressured to do things that are not kosher. Is my interpretation correct?”
A: “Yeah. Not just that, because also [redacted] going in and threatening, well, you’re no longer a speaker. You know, for [redacted] to say that you are trashing the rapport that that sales rep has with that office and that sales rep might have been calling on that office twice a week. And now you have an authority figure coming and saying, ”You know what? Yeah, we’re just not going to have you; you’re not going to be used as a speaker anymore because you’re just not writing as much. It doesn’t matter if you’re seeing a narcoleptic or cataplectic patient. It doesn’t matter. Figure it out. Get some more scripts. “I think the referral process was flawed, honestly, from the very beginning. You want to compensate your commercial sales team for prescriptions coming in, not just referrals coming in. I mean, how can you sustain doing that?” - Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
He further alleged that when some sales reps brought the abuses to the company’s attention, the regional managers would simply rotated to other territories: “there were other sales directors like that too, absolutely…what would happen is their sales reps would push back, and they would just move that sales rep to somewhere else. I’m not kidding. I saw that happen twice because of what they were doing.”

Reps pushing reimbursement staff for info to enable off-label scrips; regional managers pushing this would simply be rotated to other territories if sales reps pushed back

Q: “What were some of these things that you and other people were getting pressured to do that you weren't comfortable with—ethically or legally or whatever?”

A: “Providing insight into which of these patients—okay, that patient was off-label, well, what indication did they write? Well, you're not supposed to know that. What was it? It was excessive sleepiness, or it was this indication. Okay, well, so what do they need to do to get--? I don’t know. For me to tell you what they have to do to get that patient to cataplexy—”

Q: “So, you're saying the entire field was basically engaging in this game of trying to push off-label uses and essentially trying to come up with any indication to get the drug approved, which is off-label, essentially.”

A: “They were just trying to get referrals. That's it. Just trying to get the physicians to write the referral for Wakix. That’s what they were getting paid on.”

Q: “But you're saying that they're willing to do whatever it takes to make that happen?”

A: “I didn’t say all of them. I said there were a few that just - yes. I wasn’t comfortable with it.”

Q: “When you said it wasn't everybody, you're just referring to this one sales manager or were there other bad apples like that?”

A: “Oh, there were other sales directors like that, too, absolutely. What would happen is their sales reps would push back, and they would just move that sales rep to somewhere else. I’m not kidding. I saw that happen twice because of what they were doing—”

- Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
Ominously, he stated that Harmony is now planning to bring the field reimbursement function in-house versus contracting it to a third-party provider with managers dedicated to Harmony. He stated that the move would intensify pressure on reimbursement to assist the off-label scheme: “they’re going to be super-pressured now because the regional sales managers will be their boss…what kind of pressure do you think they’re going to get now?” He stated the move would be highly unusual vs. other pharma companies, eliminating any remaining checks and balances: “In every pharmaceutical company I've ever been associated with, the commercial team is never under the same leadership guidance as field reimbursement, ever.”

**Harmony is allegedly planning to bring field reimbursement in-house; unusual move that presages additional bad behavior**

Q: “So, RareMed is their hub?”
A: “RareMed was the hub. Harmony contracted everything as a third party, even the patient assistance was contracted out. Everything was. The only thing they had was their salespeople— I take that back—they are planning on bringing their field reimbursement in-house, which, whenever that happens, you want to talk about having pressure before whenever you were contracted to Amplity? They’re going to be super-pressured now because probably the regional sales managers will be their boss. What kind of pressure do you think they're going to get now?”

Q: “What kind of pressure is who going to get now?”
A: “The field reimbursement managers because before, remember, they were contracted through Amplity, and Amplity had their own hierarchy as far as a director to protect the field reimbursement managers and their duties. But once you roll the field reimbursement managers into the commercial team, the commercial team leadership is now in charge of field reimbursement. So, there’s no protection, and that doesn’t exist. In every pharmaceutical company I've ever been associated with, the commercial team is never under the same leadership guidance as field reimbursement, ever.” – Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
The ex-field reimbursement concluded by stating that moving the function in-house “is setting yourself up for a regulatory nightmare” and that “you just have to have that separation of church and state...I mean, it has to be segregated.” He indicated that “I’m surprised there hasn’t been regulatory pressure put on them...I’m surprised,” adding that he’s never seen abuses on this scale.

Harmony is allegedly planning to bring field reimbursement in-house; “regulatory nightmare”
Q: “So, do you think one of the reasons why they got rid of Amplity and brought it in-house was because they weren’t successful enough in pressuring you guys, so they’re trying to get their own internal people to do it?”
A: “Well, I know for a fact they were trying to get their own internal people to do it…you just have to have that separation of church and state. And if you don’t, you’re setting yourself up for a regulatory nightmare. I’ve done buy-and-build drugs, I’ve done patches, I’ve done pills, I’ve done devices, I mean, it has to be segregated, and they’re not doing it. They’re not doing it. They’re putting them all underneath the same team. I’m telling you, it’s going to be a problem. Now, one other thing I will say about the risk with these guys is it's a one-trick pony. I mean, if they ever get in trouble with Wakix, that's all they got to sell. So, if regulatory busts them, if there's a halt, if they can't market it, what are all of these people going to sell? That's all they got. Wakix is it. You know what? I apologize if I'm being a little negative, and I'm not trying to be totally negative.” – Ex-field reimbursement manager working with Harmony

“Surprised” no regulatory pressure yet; pressure to do whatever it takes to get prescriptions
Q: “The sales reps - are they still at the company?”
A: “No, they all left...yeah, I'm a little surprised there hasn't been—I'm surprised there hasn't been regulatory pressure put on them. I'm surprised.”
Q: “Because of the Stark violations?”
A: “Listen, I've worked for a lot of pharma companies, okay? And I've never seen the goofiness that I've seen with this company.”
Q: “What are some of the other areas of goofiness that we haven't talked about already?
A: “A lot of it is just the pressure to produce, I mean, very little training, if any training at all, like in [redacted’s] case, I mean, [redacted] was so mismanaged. It was just terrible. It was awful. A lot of pressure on sales, a lot of pressure on getting referrals, a lot of pressure on just getting—it was just a lot of pressure. I always kind of attributed that to it being rare and ultra-rare. I mean, how many cataplexy patients are there? Oh my god. How many are there? Get in no matter how you need to get in; get the referrals. I've never seen a company spend so much money on food. I mean, as far as entertaining and speaker's programs, like these guys do. I've never seen it.” - Ex-field reimbursement manager working with Harmony

Source: Scorpion Capital consultation calls with experts
A small, saturated market with a looming sales collapse, as sales reps struggle and run out new patients and prescribers.
We interviewed 14 ex-employees, including 8 territory sales managers. A significant number left relatively recently and indicated they receive general market color from former colleagues. They universally painted a picture of a tiny market that Harmony quickly saturated, with the trend hitting a wall 2 years after the 2019 launch. They indicate the sales difficulties worsened in mid-2022 and accelerated recently, as regions ran out of potential patients or doctors failed to see clinical efficacy, and that large numbers of previously successful reps have been placed on PIP’s – Performance Improvement Plans. One ex-sales manager stated that “morale amongst the salesforce is really low…it’s not a happy environment…it’s a pretty sour environment,” and indicated increasing management pressure: “there’s certainly more pressure…I’ve heard that they are struggling.” A second used his territory as an example, stating that his “volume of scripts was steady” but maxed out in mid to late 2021, as there’s a limited number of patients and many don’t want to switch medications, in addition to insurer pressure on doctors.

“Morale amongst the salesforce is really low”; “heard that they are struggling”
“I will say, I think for what it’s worth, morale amongst the salesforce is really low…It’s not a happy environment. It’s a pretty sour environment…I think there’s certainly more pressure—it started to come down from what I’ve heard that they are struggling.” – Ex-Harmony territory manager for a large region, previously at Jazz Pharmaceuticals

Some regions already peaked in terms of prescriptions in late 2021
A: “The volume of scripts was steady. Like I said, I had built up a pretty good base on physicians that I could get the 15 prescriptions per quarter. And the territory itself just should have—I don’t know if it has—but should have been able to sustain that. There’s no large amount of patients with excessive daytime sleepiness or cataplexy, and a lot of patients don’t want to convert from a competitor medication to use ours. And then insurance, like I mentioned. So, it’s pretty steady from when I was there. I increased it probably—when I first came in the territory, I was getting anywhere from two to five scripts, and then I gradually built it up to 10 to 15. I think that’s probably where it will probably max out.
Q: “When did it max out in your territory? What was the point?”
A: “Probably the second or third quarter of 2021.” – Ex-Harmony territory manager for a large region Florida and another state

Source: Scorpion Capital consultation calls with experts
They described a predictable pattern - an initial flurry of interest for a new drug followed by reality within two years, as the few doctors willing to try it ran out of patients or soured due to lack of clinical efficacy. A third ex-territory manager detailed what occurred in his region. A high volume prescriber who carried his territory – a “whale” and of course a speaker – put as many patients onto Wakix as he could the first year, but “he had much less the second year…they get through their patient deck and they’re like, I don’t have any more patients…I tried it on everybody.” The rep stated that this whale was “getting a lot of heat from the insurance company” and wasn’t “seeing the results that he wanted to see from…patients he had put on it.”

Whale prescribers cutting prescriptions as they run out of patients or have no clinical results or “heat” from insurers

Q: “How many Wakix scripts did he [the only whale prescriber in the territory] write, or how many patients did he have on at a time roughly? And does he still use it? Are you still in touch with him?”
A: “That launch year, I think he had like 12 patients. So, I think he had like four a quarter. And when we launched, the message was we’ll get your patients that are on medication that are not doing well. So, I think he had 12 the first year, and he had much less the second year because a lot of doctors when a new drug comes out, they’re looking for patients, and then they get through their patient deck, and they’re like, I don’t have any more patients. I’ve tried it on everybody. It was definitely less.”
Q: “You said he had about 12 the first year. How many did he have the second year?
A: “In June, when we launched, he had a couple, and then he picked—I’m going off memory—and then he tapered back. I think he was getting a lot of heat from the insurance company right there at the end of 2020, end of 2021, and he scaled back quite a bit. He was going with about four patients a month, and this is average, just depending. And then it dropped off there at the end when I was leaving there. I think he was getting some pushback, probably from the insurance companies. I don’t think he was seeing the results that he wanted to see from these patients the he had put on it.” – Ex-Harmony territory manager for a large southeast region across two states

Source: Scorpion Capital consultation calls with experts
A fourth ex-territory manager characterized Harmony’s current situation as “very difficult” – “They’re going to run out of narcoleptic patients. They’re just not seeing that many patients…It's very difficult…we got all the low-hanging fruit.” He described territories like his which had a speaker who “blew it out” with new prescriptions after launch, but with the trend abruptly reversing and crashing “back down to earth” as patients discontinue Wakix, with new ones hard to find: “…and then, he ran out of patients.”

Running out of patients; “it’s very difficult”
“Yeah, you needed more than one or two guys that would dabble with it. You’d have a guy who’d put three or four on a quarter—that’s a really good doc. And then you needed to come up with the rest through ones and twos, and maybe you’d have a guy—to me, and each territory is so different—with me, I would have a guy put three or four, and that person would rotate because, again, a rare disease, they’re going to run out of patients. They’re going to run out of narcoleptic patients. They’re just not seeing that many patients. So, you’d have to go find somebody else and put four or five. It’s very difficult. And as time went on, we got all the low-hanging fruit. Now, you’ve got to go out, and you’ve got to get them to really search. Long story: I’d have probably one or two guys where I get three or four, then I’d have to make the rest up with ones and twos. So, the total number of physicians that I would call would be 125, somewhere around that, of which probably 3/4 of that would not write a script for the entire quarter, any given quarter. I am really trying to be fair here, too. I’m not trying to just rain on Harmony. I’m really not.” – Ex-Harmony territory manager for an eastern state

Territories suddenly reversing and crashing “back down to earth” as patients discontinue and new ones are hard to find
A: “Yeah, we blew it out. I, particularly, really blew it out. I had one of my speakers, [name redacted], he just, god, every day he put two people on. He wrote 38, I think is what my memory serves, in the first quarter. And I told you four or five is big. He wrote 38 in one quarter. My first bonus check was over 50k for one quarter. The second quarter, same deal. And then, he ran out of patients.”
Q: “Are you still in touch with him? How many patients does he have now?
A: “…I don’t know if he knows, to be honest. Not too many. I know the rep that ended up with him, and he told me he was writing about one or two a quarter for him.”
Q: “Was that common that there was this big spike, and then it came down?”
A: “Yeah, because you have something new. You had a disease state that’s very difficult to treat. So, they’re looking for something else, and yeah, when we launched, they put them on, and then they came back down to earth.” – Ex-Harmony territory manager for an eastern state

Source: Scorpion Capital consultation calls with experts
A fifth former territory manager stated that as reps began to struggle in mid-2022, Harmony started putting them on Performance Improvement Plans – known as PIP’s – an ominous move that typically indicates sales are far below quota and signaling potential termination: “they instituted a lot of those over the last few months…I’m still very friendly with a few people there…I heard that quite a few of them were handed were handed out.” The rep indicated that Harmony keeps increasing quotas – to hit quarterly expectations, presumably – but that the numbers “make no sense whatsoever” versus the number of potential narcolepsy patients: “the numbers keep increasing, but the patients are going down.”

Recent increase in PIP plans as sales reps struggle; sales numbers Harmony is pushing are unachievable
“It was a bit of a toxic culture. In the Northeast region alone, my old team, 8 people have left. So, it’s kind of a little bit of a revolving door. The management is very numbers-driven, which makes sense. Obviously, they need to make money; they are now a publicly-traded company, as you know. So, they have instituted things like—I don’t know if you’ve heard the word PIP, but it’s a performance incentive plan—it’s to increase your performance. So, they instituted a lot of those over the last few months at the company because I’m still very friendly with a few people there…You have to remember, it’s rare disease. So, the number that Harmony upper management is putting out like even in my territory, which was [state redacted], the amount of prescriptions that I had to get in a quarter was more than the rep in Manhattan had, which actually makes no sense whatsoever. But I don’t know what methodology they were using to figure that out. While my geography may have been bigger, obviously, there are more people and potential for a patient in a geography like Manhattan because there are just more people there. The numbers never matched up to me.” – Ex-Harmony territory manager for several states in the Northeast

Increase in PIP plans allegedly began in mid-2022; patient counts are tanking while sales targets keep increasing
Q: “You said they put a lot of people on these PIP plans, in the last few months. What’s your interpretation of that?”
A: “That’s what’s happening with the reps. The numbers keep increasing, but the patients are going down. We’re not going to have more of these patients..”
Q: “Has the PIP plan prevalence changed a lot recently? Has it accelerated?”
A: “Yeah, I heard of a couple of them and then this past year they had a meeting in June or something like that and right after that meeting, they started handing out performance—and I was just like, oh my god, how do you have a meeting because usually, these meetings are like, they’re rah-rah meetings. They want to get you excited about talking about the product again. You go out of there kind of energized. And then, to get a PIP notification is not very motivating after having a meeting like that..I heard that there were quite a few of them that were handed out, and I don’t know the number.” – Ex-Harmony territory manager for several states in the Northeast

Source: Scorpion Capital consultation calls with experts
Two other ex-territory managers corroborated the recent spike in Performance Improvement Plans, stating that even Harmony’s top territories and performers are now hitting the wall. One stated he spoke to a current sales rep who was “top 15 in the company and this year [2022], he had two bad quarters, and they slapped him with a performance improvement plan.” He implied that Harmony is now at the stage of trying to squeeze blood from a stone and “getting even more aggressive than they did before…and he’s a good rep.” Another ex-manager provided his own similar experience, stating that his performance “did fall off…my performance did slip off for that quarter, but in previous quarters I had done well.” He added that is now common with previously successful reps: “yes, there were a lot of representatives” where “their performance had fallen way off.”

*Top performing sales reps now suddenly being put on PIP’s*

“There’s someone I talk to that the previous year, *he was like top 15 in the company and this year, he had two bad quarters, and they slapped him with a performance improvement plan*. He’s like, what? He had a doctor that was a psychologist—this was one of those whale doctors that I talked about…he was like, this is crazy. He’s like, I performed really well last year. What’s going on here? *It seemed like they were getting even more aggressive than they did before. And he’s a good rep.*” — Ex-Harmony territory manager for a large state in the Midwest

“*Lot of* sales reps have performance that has “fallen way off”

“So, it did fall off…*my performance did slip off for that quarter, but in previous quarters, I had done well. Yes, there were a lot of representatives that their performance had fallen way off*. My question is, the very successful territories had speakers in them and, you know, when you pay somebody to do talks for you, you tend to get—it’s harped upon, it cannot be quid pro quo but, let’s be honest, to a degree, you pay somebody a stipend to do a talk for you, and you continue to do that, they tend to look to use your drug. I’m not saying that they’re going to use it in inappropriate places, but they look to use your drug more frequently. So, those people were successful.” — Ex-Harmony territory manager for an eastern state

Source: Scorpion Capital consultation calls with experts
Yet another former territory manager conveyed a flattening in the last 6-12 months in particular, with large numbers of sales rep now floundering: “Yeah, it was definitely slowing down. The way you could gauge that would be the pressure that was applied from above, the flattening out of the trend...definitely, there was a flattening...but the company and the powers that be did not want to hear it.” Confirming the spike in Performance Improvement Plans, he estimated that a significant percent of sales reps are below quota – “the percentage of representatives that I knew that received no payout was increasing” - saying the dynamic started “probably 18 months to a year ago” but has recently accelerated: “when I was leaving, quite a few...and quite a few now.” He stated that on his team, 3 out of 7 reps won’t get paid, stating it’s now a “mature product” and “quotas got way too high” – “all the low hanging fruit is gone.”

Flattening in the last 6-12 months in particular, with large numbers of reps now suddenly floundering
Q: “Was there any evidence that since you just left recently, that the number of new scripts or patients is slowing down?”
A: “Yeah, it was definitely slowing down. The way you could gauge that would be the pressure that was applied from above, the flattening out of the trend. You serve a niche, you get all the patients from that market and then it's gone to flat. Definitely, there was a flattening, which would be expected, but the company and the powers that be did not want to hear it.”

Q: “When was the flattening?”
A: “I would say probably about a year ago. Something along those lines. Maybe even 18 months ago.”

Q: “And what other signs were there that there was a flattening?”
A: “Just really basing it on national performance, and at Harmony, as a representative, you didn't make a nickel until you hit 70% of your goal. So, if your goal was 10, you had to have 7 before you'd make a nickel. If you hit 6, you made no dollars for a bonus payout. So, the percentage of representatives that I knew that received no payout was increasing.”

Q: “And when did it start increasing?”
A: “Probably 18 months to a year ago, you'd see more but really, when I was leaving, quite a few. And quite a few now, I think, the team I was on—let's say there are 7 reps—I think probably 4 will make money and 3 will not.”

Q: “And how prevalent is that across different territories right now?”
A: “This is a guess, but I would say 30 to 35, maybe—30% of the representatives won't make any money because they didn't hit that 70% threshold...yes, the quotas got way too high. Way too high. How am I going to increase a mature product, it’s been on the market for a while, and all the low-hanging fruit is gone. How am I going to increase quarter over quarter by 40%? No one could have done that...nobody could do 40% with a product that mature.” – Ex-Harmony territory manager

Source: Scorpion Capital consultation calls with experts
Doctors, particularly high volume prescribers and speakers for Harmony, provided the same color as territory managers as far as market saturation and patient growth hitting a wall. A KOL at one of the largest sleep centers in the US stated his Wakix starts have plummeted vs. other drugs: “my prescribing of Wakix has really started to peter off quite a bit.” He indicated he only started 5 patients in 2022 vs. 80 on modafinil, 40 on venlafaxine/bupropion, 30 on amphetamines, 15 on sodium oxybate, and 8 on Sunosi. He stated Wakix “really hasn’t taken off” – “it’s just not as effective as we wanted it to be...and I was somebody who was pretty bullish on it…I really liked the idea of it.”

**KOL at one of the largest centers in the country says his Wakix starts have plummeted vs. other drugs**

Q: “And how many patients did you prescribe it to in 2019, 2020? Like all 20 right off the bat?”
A: “Probably half of my prescriptions came out in that first 12 months, whenever that was. That was my first - 10 prescriptions came out at that time, and then the rest of them kind of trickled out slowly. Certainly, the majority of the prescription for narcolepsy Type 1 were in that first year. I don't remember exactly. Let's say the last couple of quarters of '19; that's about when it came out. The first quarter of '20, and then, of course, everything just halted in '20. From the second half of '19 to the first half of '20, that was 10 patients. The numbers for the rest of 2020 were low, but that has more to do with covid than anything else. And then, from 2021 until now, which has been two years, my prescribing of Wakix has really started to peter off quite a bit. How many have I prescribed this year? When I've seen a whole ton of patients because our clinic, we're quite a bit busier now than we were for a while, five...In comparison, for 5 prescriptions of Wakix, I probably prescribed—these are new scripts, this is not old people but new scripts, probably 80 with modafinil/armodafinil. I am not distinguishing between those two. Venlafaxine/bupropion would be probably about 40. Sunosi, I prescribed about 8 times. Amphetamines, all the amphetamine class, probably 30 times. And then, in the last year, how many times did we prescribe an oxybate as a new script? Let's say 15, and the majority of those have been sodium oxybate, not low-sodium Xywav.” – Physician and professor of neurology at a large academic center; 120 narcolepsy patients

“Drug really hasn’t taken off...and I was somebody who was pretty bullish on it”

“Here’s my honest take on it. You can tell I'm not a huge fan of this drug...Now, it's possible the reason why I don't know that is because since this drug really hasn't taken off, we haven't really seen all of the people who might otherwise have had pretty bad, horrific side effects from it, like hepatic failure or something like that because those patients are so few and far between it hasn't hit our radar. But I actually don't think that's likely. More likely, I think it's just not as effective as we wanted it to be. And I was somebody who was pretty bullish on it. I really liked the idea of it.” – Physician and professor of neurology at a large academic center; 120 narcolepsy patients

Source: Scorpion Capital consultation calls with experts
A prolific speaker for Harmony who we believe to be one of their top two or three prescribers in the country stated Wakix is tapped out and won’t grow much from here: “I don’t know that it’s going to grow much…compared to the percentage of the market it already had”; “any monumental growth that it was going to make probably would have happened by now…it’s probably just going to keep doing kind of what it’s been doing.” We asked him who Harmony’s largest prescribers are in the US, and he rattled off their names and evinced knowledge of their prescribing patterns, leading us to believe that they share his view that Harmony has hit a wall. A second prescriber with a large practice at a leading academic center said only 5 of his 40 narcolepsy patients are on Wakix, but that “I have not started anyone” new on it in about a year.

**Speaker and one of Harmony’s highest volume prescribers says Wakix won’t grow much from here; tapped out**

A: “I think Wakix—I don’t know that it’s going to grow much—I don’t know how much it’s going to grow compared to the percentage of the market it already has.”

Q: “Do you think it’s kind of saturated and tapped out?”

A: “I don’t know if it’s tapped out. **I think that any monumental growth that it was going to make probably would have happened by now. I think it’s probably just going to keep doing kind of what it’s been doing.** That’s what I think.” –Neurologist who is a speaker for Harmony and one of their highest volume prescribers

**KOL and professor at a leading academic sleep center hasn’t started a new Wakix patient in a year**

A: “I’ve got about safely 30, probably about 40 narcoleptic patients, which is sky-high. That’s probably 10x more than most people.”

Q: “How many patients do you have on pitolisant now?”

A: “My grand total right now is about **five out of 40.**”

Q: “And was it higher before? Walk me through what your mindset was at the beginning, what changed, and why it’s only five now.”

A: “At the beginning, I was never super-excited by it because I heard rumblings out of Europe that it was just an average drug. So, I never heard that it was an amazing drug, to begin with. I didn’t have super-high expectations. I will say that the patients were excited by it initially. Sunosi had come around at the same time, but everyone was excited about Wakix, and because it was just different, I guess. I wasn’t getting the best results…it wasn’t like a wow like they get with Xyrem. For me, the Xyrem is just so effective that it just pales in comparison to that. So, I relegated it pretty early on to my Xyrem failures or Xyrem intolerance…**My last start on Wakix was probably late last year or early this year. I can’t recall; it’s been a while, and we’re at the end of this year. It’s been almost a year, I have not started anyone.**” – Neurologist and professor at a large academic institution

Source: Scorpion Capital consultation calls with experts
We asked every doctor we spoke to what their peers and colleagues think of Wakix, and if there’s any buzz or enthusiasm at medical conferences and so forth. The feedback was unequivocal that it’s a flop: “the excitement for this is on the wane”; “we were fairly eager and excited…and then quite disappointed”; “I don’t anybody who’s really bullish on it” and that at best they “kind of prescribe a little bit here or there. Another at a large center stated that if the Harmony rep wasn’t proactive and bringing lunches that “it would be just dead” in his practice, and that the few patients he has on it are only because he has so many patients who fail other drugs that he threw a few onto Wakix as a Hail Mary.

“Excitement for this is on the wane”; previously excited doctors now “quite disappointed”
“I think the excitement for this is on the wane. The peak excitement was right before we started prescribing it, and then realized that there was going to be a centralized pharmacy, and the fact that they were pricing it so high was going to take all the convenience away of the lower FDA Schedule…the question you asked me was, what is the impression on behalf of sleep specialists? This was something that we were fairly eager and excited about, and then quite disappointed by how the burden of prescribing has really interfered with our ability to get people on it.” – Physician and professor of neurology at a large academic center

“I don’t know anybody who’s really bullish on it”; just prescribe “a little bit here or there”; no one “loves” Wakix
“I’m thinking in my center and the other large hospitals in the [major metropolitan area, redacted]; I don’t know anybody who’s really bullish on it. I know people who, like me, kind of prescribe a little bit here or there, but I don’t know anyone who just is like they love this agent. That’s not the case, like if you ask me about Xyrem or Xywav, I can point to you people; I’m like, I think they prescribe it to everybody.” – Physician and professor of neurology at a large academic center

KOL at one of the largest centers in the country has no idea what it costs, VA patients
Q: “Do you hear any buzz about this drug when you go to conferences?”
A: “I think if they didn’t have a strong rep, it would be just dead. The thing about sleep medicine is if something works well, it really sticks. It's an okay drug. If I had four or five narcoleptics, I'd have zero people on Wakix. Does that make sense? It's because I think I have so many.”
Q: “What do you mean there?”
A: “I'm saying I have so many that some have failed the other stuff.”
Q: “And that's the only reason they're on this?”
A: “Yeah. No one's a first-time person.” – Neurologist and professor at a large academic institution

Source: Scorpion Capital consultation calls with experts