ABIVAX SA (NASDAQ: ABVX)

A Biotech Fraud For The Ages: How A Cytotoxic Mass Action Compound – An Extreme Lipophile In the Range Of DDT, Dioxin, And Persistent Organic Pollutants -- Fooled The Public With A Fictitious Mechanism Of Action And Suspect Foreign Trial; Our Independent Lab/CRO Studies Suggest A Fatally-Flawed Molecule With Severe Drug Liabilities And Evidence Consistent With Long-Term Carcinogenicity.

- **Experimentally-measured LogP and pKa -- by academic laboratories serving as our CROs -- lead us to conclude that obefazimod's chemistry is consistent with a lipophilic carcinogen, with an aberrant mass action, off-target, membrane-partitioning profile in stark contrast to its purported, novel "selective" "miR-124 upregulation" MOA via "CBC binding"**
- **Obefazimod's lipophilicity – undisclosed by ABVX -- is similar to many banned or restricted pesticides and industrial chemicals, due to their long-term tissue accumulation profiles; it is so extreme that is not even measurable by standard lab methods, leading us to seek out one of the few labs globally with specialized equipment to assess such an outlier compound**
- **Our laboratory experiments demonstrate that obefazimod has the potential to be a photocarcinogen -- at one of the most concerning wavelength bands for photoactive drugs. The drug absorbs UVA at 8.4× the ICH photosafety screening threshold.**
- **ABVX's skin-safety disclosures raise disturbing questions of potential under-reporting, inadequate surveillance, and questionable, conflicted central adjudication – per interviews with ex-employees closely involved in Phase 3 safety oversight**
- **Obefazimod aka ABX464 exhibits significant anti-parasitic/nematocidal activity – consistent with its mass action signature -- and has thus recently been studied as a potential new class of anthelmintic drug for livestock; its tissue accumulation profile in man is troubling vs. the cytotoxicity threshold at which it kills parasites, per our PK analysis/models**
- **We are skeptical it is safe even for livestock, given a buried 28-day monkey toxicology study that stopped dosing early in every treated group and sacrificed moribund animals -- "the main target organ of ABX464 toxicity was found to be the gastro-intestinal tract" – a finding difficult to reconcile with a "readily metabolized and non-toxic" UC drug**
- **Phase 3 reliance on China is a black hole. Listed sites, like military hospitals, include those implicated in executed-prisoner organ sourcing or study/data fraud. Ex-employees on the secrecy: "this is something even my team had no visibility…that was a big black hole for me…they just told me it's operating differently…they didn't need me or my team there…"**
- **ABVX's scientific foundation and key claims rest on a cesspool of heavily contaminated, retracted publications by Chinese paper mills – its presentations have long-cited a now-retracted paper central to its purported mechanism. The co-founder and "inventor of ABX464" exhibits a troubling history of phony claims, retracted science, and ongoing red flags for data integrity**
- **Foundational papers/assays that underpin ABVX's mechanistic and safety claims are irreproducible, per our lab studies**

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This report, inclusive of any of its research and findings published or presented in the format of related scientific abstracts, contains original scientific research, independent laboratory findings, reanalyses of published and publicly available scientific data, and Scorpion Capital LLC's interpretations, hypotheses, and opinions concerning ABVX, obefazimod, and related scientific and clinical matters. Our scientific conclusions represent our good-faith interpretations of the evidence, based on the sources, methodologies, experimental results, assumptions, and limitations discussed herein, and concern matters that may be subject to legitimate scientific uncertainty, disagreement, and ongoing debate. We do not represent that our interpretations are definitive or universally accepted, and acknowledge that other researchers may reach different conclusions from the same evidence.

In connection with our scientific research, we retained and compensated third-party scientists and laboratories, including researchers affiliated with academic institutions that we believe to be reputable, to conduct experiments and analyses. Although we exercised reasonable efforts to oversee their work and assess its quality, and believe their methods and procedures to be consistent with accepted scientific standards, we have not independently verified every aspect of their work and cannot and do not make any representations or warranties regarding the accuracy, completeness, reliability, or reproducibility of their instruments, calibrations, protocols, data, results, or adherence to our specifications; furthermore, although compensation was agreed upon in advance and was not contingent upon any particular findings or outcomes, such third parties may have financial or other conflicts of interest, biases, or incentives that could influence their work or reporting.

Throughout this report, references to information, data, results, protocols, or other materials as "undisclosed," "unreported," "unavailable," or similar terms mean only that we did not identify or locate such materials through our good-faith searches of the scientific literature, regulatory filings, corporate disclosures, and other sources reasonably available to us, and should not be construed as categorical assertions that such information does not exist, has never been disclosed, or could not be located through other means. Where we identify apparent inconsistencies, methodological deficiencies, irreproducible findings, statistical anomalies, or potential scientific misconduct, such assessments reflect our interpretation of the available evidence and should not be understood as findings by any court, regulatory authority, or independent investigative body unless expressly stated otherwise. Our experimental and analytical findings do not, by themselves, establish clinical causation in humans or the intent, knowledge, or state of mind of any person. Except where expressly indicated, our research and analyses have not been independently peer-reviewed, and we cannot guarantee that subsequent research or additional data will confirm our findings. We encourage independent scientific scrutiny, replication, and debate, and our interpretations and conclusions may change in light of additional evidence.

The principal individual responsible for the research, analysis, and preparation of this report is Gurkirat Kahlon, Founder and Chief Investment Officer of Scorpion Capital LLC.

PART I. Introduction to the real Abivax

Chapter 1. An 11-month investigation -- our longest and most intensive research effort to date (*p11-40)*

ABVX - a long-flailing French microcap, for most of its history – is a revolving door with two CEO's and five Chief Medical Officers in recent years, with its stock now fueled by bagholder delusions of FDA approval and acquisition grandeur. Our research encompassed a wide-ranging review of ABVX's publications/data and statistical methods; independent laboratory characterization of obefazimod; interviews with ex-ABVX executives/employees and those of its CROs; and an extensive analysis of the scientific literature.

Chapter 2. Abivax's origin story (*p41-49)*

ABVX is the latest pump by a controversial, serial French life sciences promoter with a history of dubious, failed microcap stock promotions that make grandiose claims, only to end in safety-related recalls, fatalities, regulatory/media scrutiny, and stock collapse.

Chapter 3. The scientific rot at ABVX runs deep *(p50-58)*

Co-founder Jamal Tazi -- "the inventor of ABX464" – exhibits a troubling history of phony claims, retracted science, and ongoing red flags for data integrity and conduct, which continue to be flagged by independent sleuths. He is the senior author on every key ABVX paper – the entire corpus and key claims revolve around Tazi's small group.

Chapter 4. A scientific foundation built on retracted Chinese paper-mill "science" *(p59-65)*

ABVX's scientific foundation and key claims rest on a cesspool of heavily contaminated, retracted publications by Chinese paper mills – its investor presentations have long-cited a now-retracted paper central to its purported mechanism. The single-miR disease mechanism space -- miR-124 in particular – exhibits one of the most rampant research fraud epidemics in science. We found 63 retracted miR-124 papers, of which 8 are STAT3 papers -- ABVX's verbatim mechanistic chain and anti-inflammatory story, leading us to suspect that Tazi's group simply lifted the drug's fake, contrived miR-124 upregulation narrative from these compromised, now-retracted Chinese papers.

PART II. Extreme physical properties of obefazimod classify it as a highly lipophilic membrane toxicant – one of the most lipophilic drugs ever advanced to Phase 3

Chapter 5. Obefazimod's extreme physicochemical properties *(p66-77)*

The molecule's outlier characteristics -- such as its logP/pKa -- dictate its abnormal pharmacokinetic and toxicity profile, predictive of tissue loading, broad off-target effects, and aggregation. Most key properties lack disclosure, per our search, so we measured the metrics ourselves. Its computed logP of ~6 implies a million-to-one preference for lipid compartments over aqueous ones; our CRO experimentally measured a logP of 6.35 -- higher by almost 3X (log scale). High-logP compounds are driven out of water and into lipid membranes, fleeing plasma to bury into every lipid-rich compartment, from cell membranes to adipose tissue to the brain, driving tissue accumulation.

Chapter 6. The drug's characteristics violate virtually all landmark drug-likeness screens/rules for viability and safety *(p78-89)*

The unequivocal textbook consensus: lipophilicity is THE primary physicochemical determinant of drug quality, as noted in a seminal paper cited 3,000 times: "most important drug-like property," driving off-target promiscuity and toxicity. Obefazimod sits squarely in the red-alert zone across the most well-known screens: Rule of 5 (Lipinski), 3/75 (Pfizer), Rule-of-Two (FDA), Waring, and others. Breaching these rules predicts drug failure and numerous, independent toxicity mechanisms: mitochondrial toxicity, liver injury, hERG/cardiotoxicity, phototoxicity, and other liabilities.

Chapter 7. Obefazimod's lipophilic liability is virtually unprecedented among FDA-approved drugs and within UC comparators specifically *(p90-99)*

There is almost no FDA precedent for a small molecule with logP > 6 chronically dosed at the levels studied. The drug is an outlier even among a narrower set of FDA-withdrawn high-logP drugs. Its comparator space is a graveyard, with only a few orphan, oncology, or niche/exotic drugs where the alternative is death -- with boxed warnings, heavy monitoring, and/or FDA withdrawal. We counted ~1,200 NDA approvals in the last decade and only 18 at LogP ≥ 6 – each has a mitigant except obefazimod, which is an even more extreme outlier as it is neutral + low TPSA, further magnifying the safety hazard.

Chapter 8. The combination of properties – logP, TPSA, and others -- is unusual for a drug but resembles the signature of persistent organic pollutants (POPs) and certain agrochemicals *(p100-110)*

High lipophilicity is a core feature of pesticides, enabling penetration of membranes which are lipid layers. The agricultural chemistry literature indicates a logP > ~3 is hazardous even for a pesticide, driving binding to "hydrophobic targets, increasing risk of nonselectivity and toxicity" and environmental persistence/bioaccumulation. A logP ~6 is 1,000X more lipophilic than logP 3 (log scale). We note that the drug's molecular fingerprint shares key similarities with classic agrochemicals.

PART III. Pharmacokinetics, enterohepatic recycling (EHR), prolonged tissue loading – a red-alert PK signature that magnifies toxicity and risks extensive FDA scrutiny

Chapter 9. Obefazimod's own PK data undermine its purported "short half-life" story *(p111-122)*

The drug appears to disappear from plasma because it is redistributing into tissue -- not because it has left the body. Glaring omissions and inconsistencies in published PK data obscure the true extent of tissue sequestration, prolonged persistence, and cumulative toxicity risks.

Chapter 10. Obefazimod appears to undergo extensive enterohepatic recycling – repeatedly regenerating parent drug and reloading tissue. We could find no disclosure admitting EHR. *(p123-127)*

Multiple independent PK anomalies point to a classic EHR signal and hidden recycling loop; drug exposure collapses when the suspected pathway is disrupted; critical studies and disclosures are missing, potentially concealing far greater long-term tissue exposure and toxicity.

Part IV. The real mechanism of action: mass-action membrane toxicity, cytotoxicity, and broad antiparasitic/anthelmintic activity – masquerading as a selective anti-inflammatory UC drug

Chapter 11. Mass action membrane toxicity/narcosis – the drug obeys the Meyer-Overton law *(p128-135)*

The membrane itself appears to be the drug's target, as it exhibits nonspecific toxicity in parasites and human cells, in accordance with the classic law. Independent studies demonstrate PI3K/AKT blockade – also consistent with mass-action, not the purported selective miR-124 expression mechanism. Even ABVX's own assays point to this alternative mechanism.

Chapter 12. Cytotoxicity, slowed cell division, mitochondrial failure -- ABVX's "non-toxic" claims collapse under scrutiny *(p136-149)*

Our independent lab tests expose a deeply flawed foundational safety assay – actual drug concentrations were ~5× lower than reported, artificially inflating its purported safety threshold. ABVX's own data reveal impaired T-cell proliferation; independent assays show severe mitochondrial toxicity; a monkey toxicology study stopped dosing early in every treated group, with moribund animals. Its purported efficacy concentrations overlap with cytotoxicity and aggregation,

Chapter 13. Obefazimod exhibits the profile of a broad-spectrum anthelmintic/nematocide *(p150-157)*

Independent studies demonstrate toxicity across parasitic species and multiple unrelated protein targets; alarming implications for off-target toxicity and long-term tissue accumulation, with little evidence of a meaningful safety margin. Comparable antiparasitic agents are generally dosed briefly to limit toxicity - our modeling suggests prolonged dosing could accumulate tissue concentrations approaching those toxic to parasites, raising alarming safety questions.

PART V. Abivax's purported mechanism of action – enhancing miR-124 expression which then normalizes inflammation – is simply a fraud

Chapter 14. The "miR-124 upregulation" illusion *(p158-185)*

ABVX turns virtually zero miR-124 expression into spectacular "upregulation" through statistical sleight of hand and misleading investor charts. Independent expression databases and its own studies agree that mature miR-124 is not even expressed in blood, immune cells and gut – undermining its MOA which requires functional miR-124 in peripheral immune cells. ClinicalTrials.gov records point to highly suspect scientific conduct -- blood values replaced with numbers ~60 million× larger; missing endpoints, contradictory units, and extreme statistical anomalies. The Even Phase 3 placebo arms show 10-fold variability.

Chapter 15. The purported miR-124 mechanism is a molecular bait-and-switch – the real signal points to AhR activation and inactive host RNA, not selective CBC binding *(p186-200)*

Our reanalysis of Abivax's own human RNA-seq data shows that the entire drug-induced "miR-124" signal is the host transcript LINC00599 -- not mature miR-124. Moreover, independent third-party data place the "miR-124" signal downstream of AhR -- an AhR antagonist reverses ABX464's entire effect, at odds with ABVX's claimed CBC binding mechanism. ABVX repeatedly conflates inactive LINC00599 host RNAs as active mature "miR-124" across its papers, with its own data showing that the drug neither increases splicing nor miR-124. Our independent lab experiments indicate the foundational CBC-binding evidence is an aggregation artifact, undermining ABVX's entire purported mechanism.

PART VI. Obefazimod chronically activates AhR, a well-documented carcinogenic pathway. Given its extreme lipophilicity and tissue-loading profile, chronic AhR activation + lipoprotein transport creates the potential for devastating carcinogenicity.

Chapter 16. Independent pharmacology and ABVX/Tazi's own datasets indicate obefazimod is an AhR agonist -- a core mechanism absent from ABVX's MOA narrative *(p201-210)*

The company's own data clearly establish coordinated AhR activation -- all six prespecified AhR genes rise with ABX464. Third-party researchers have demonstrated near-maximal AhR activation, confirmed by our reanalysis of Abivax/Tazi's own data which indicates another extraordinary signal: the hallmark AhR gene is the #1 induced gene in human cells. Chronic tissue exposure thus has the potential to turn a normally transient, beneficial pathway into sustained tumor-promoting signaling, raising alarming long-term carcinogenicity concerns.

Chapter 17: Obefazimod's lipophilicity + AhR activation converge on a disturbing potential mechanism for cancer promotion *(p211-224)*

Our count identifies 17 malignancies across Phase 2/3, including 16 on active drug; lipoprotein transport may preferentially deliver drug into tumors and precancers. Independent experiments show that weakening AhR's tumor-suppressive feedback accelerates malignant behavior and produces up to 7× tumor growth. Studies show that many adults already harbor occult cancers, precancers, and premalignant cell clones that a tumor promoter could accelerate - skin precancers affect ~40–60% of sun-exposed adults >40, Chronic AhR activation provides a plausible mechanism for promoting or progressing these pre-existing lesions into active malignancies.

PART VII. Skin cancer and phototoxicity – an alarming clinical safety signal. A lipophilic drug is predicted to extensively partition into skin tissue, placing photoexcited molecules near oxidizable membrane lipids. The FDA requires tiered photosafety studies in the NDA package for such drugs – we are curious if ABVX conducted any.

Chapter 18. Scorpion Capital's independent lab experiments indicate obefazimod's concerning potential for UVA-driven skin cancer *(p225-233)*

Our laboratory data demonstrate that obefazimod has the physicochemical prerequisites to be a photocarcinogen -- at one of the most concerning wavelength bands for photoactive drugs. The drug absorbs UVA at 8.4× the ICH photosafety screening threshold; ABVX's own protocols acknowledge metabolite phototoxicity; and the drug's extreme lipophilicity predicts strong partitioning into cellular membranes once the drug reaches skin, potentially placing a photoexcited molecule near oxidizable membrane lipids. Phase 3 produced 10 non-melanoma skin cancers, nine on active drug; the highest-dose signal was ~4× higher after normalization – ABVX's selective pooling and misleading benchmarks downplay the signal.

Chapter 19. ABVX's skin-safety disclosures raise disturbing questions of potential under-reporting, inadequate surveillance, and questionable, conflicted central adjudication *(p234-246)*

ABVX's recent Phase 3 maintenance data reported 68 skin lesions: 4 were identified as non-melanoma skin cancers, while the other 64 were grouped under "skin lesions, all types" with no further breakdown. Based on information from a former ABVX employee closely involved in safety monitoring, we are concerned that this catch-all category may obscure a substantial number of photosensitivity reactions. The ex-employee described numerous reactions consistent with potential photosensitivity, as well as deeply flawed monitoring, poor-quality photographs, rarely-available biopsies, delayed reporting, and questionable adjudication practices that cast serious doubt on the credibility of the safety narrative.

PART VIII. A highly suspect Phase 3 trial – foreign sites, questionable data integrity, inadequate safety reporting, underwhelming efficacy, flimsy US subgroup data that suggests potentially severe geographic imbalances. We expect intense FDA scrutiny, with potential risk of a Complete Response Letter (CRL) – or worse.

Chapter 20. Undisclosed level of reliance on China – the black hole in ABVX's Phase 3 trial; alarming red flags for data integrity and fraud; and recent Congressional scrutiny of Chinese sites *(p247-256)*

ClinicalTrials.gov lists ~50 Chinese sites, second only in number to the US, including military hospitals and institutions with histories of scientific misconduct and allegations of coercive organ sourcing. We found no disclosure of country-level enrollment for Asia, which was specified at 24% of total enrollment. Ex-senior employees closely involved in international trial oversight expressed shock when we asked about Chinese sites, describing a complete lack of visibility, monitoring, or involvement, even among those involved in oversight of sites in other Asian countries: "we did have sites in China…this is something even my team had no visibility…that was a big black hole for me…they just told me it's operating differently…they didn't need me or my team there…"

Chapter 21. Reliance on alarmingly poor US sites and third-tier private practices in questionable areas vs. reputable centers; sites listed in Mexico, India, Ukraine strain credibility *(257-274)*

Eastern Europe accounted for 38% of enrollment, including 15 sites in war-torn Ukraine listed on ClinicalTrials.gov. Ex-executives and employees describe appalling site selection, poorly qualified investigators, protocol violations, deficient monitoring, and an IQVIA CRO operation characterized as a "calamity of errors"; "we got the C team"; "shitty team."

Chapter 22. Purportedly blockbuster Phase 3 efficacy is remarkably mediocre – with troubling endpoint manipulation, lack of dose-response, and other inconsistencies and red flags *(p275-289)*

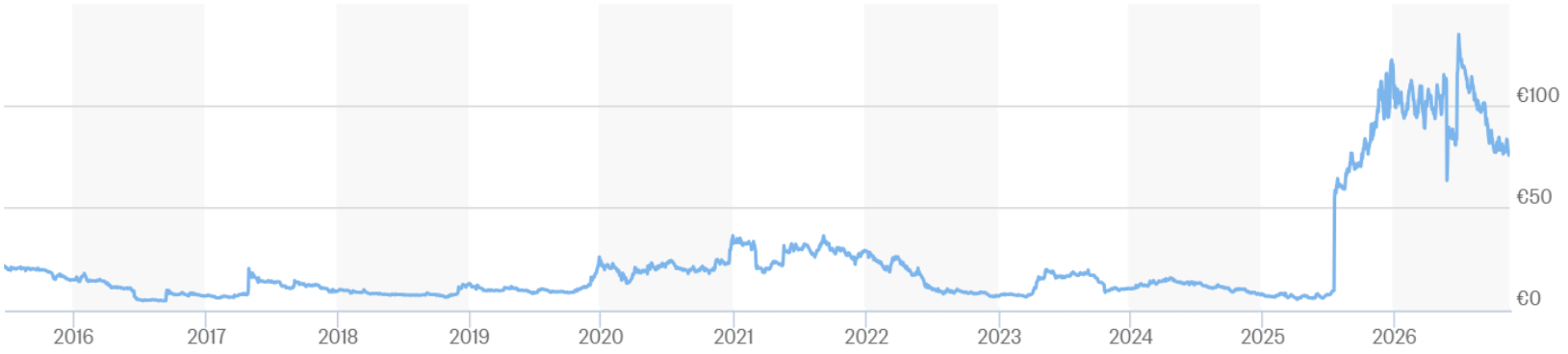
A headline 77% reduction in fecal calprotectin translated into an underwhelming 9.3% histologic remission; clinical efficacy is unremarkable versus approved UC drugs. Key histology endpoints failed, disappeared, or went unreported. Moreover, the strongest purported biomarker effects failed to translate into meaningful tissue remission.

Chapter 23. Flimsy U.S./North American Phase 3 subgroup data risks intense FDA scrutiny (p290-297)

The apparent efficacy rests on an anomalous zero-placebo result. Just 10% of Phase 3 patients were enrolled in North America; zero of 36 placebo patients achieved remission. A single placebo remitter would erase the 50 mg arm's statistical significance; objective endoscopic improvement failed, and pooled, post-hoc subgroup reporting obscured trial-level results. The only endpoints that hit are patient-reported, a pattern that typically merits FDA scrutiny: weak objective endpoint + "robust" subjective endpoint in the highest-integrity geography, ignoring the dubious quality of ABTECT North American sites to begin with.

Our favorite biotech shorts - and most successful - are frauds of the too-good-to-be-true genre. Our last report exposed SLNO – a 90 cent reverse-merger stock that had spiked 100X in ~2.5 years. ABVX is far more absurd. It first listed in Paris in 2015, struggling for years as a single-digit ~$100MM micro-cap, with a brief heyday as a "COVID cure" pump. It remained a left-for-dead ~$6 stock as recently as June 2025 – then exploded to ~$150 after Phase 3 data. We notice anomalies: the market assessed ABVX's value at almost nothing despite positive Phase 2 results in 2021, on top of a years-long "scientific" corpus – but now pegs it at $7-10B+, varying by the month. Whether driven by ignorant social media hype or late-cycle detritus floating with the speculative tide, we think this fairy tale will end with a round trip.

ABVX stock chart, French listing: 2015-present



We've selectively published three prior biotech reports: ALLK, HRMY, and SLNO -- ABVX is a contrived mash-up of all three scams. Allakos (-99%, $6.5B) was also an anti-inflammatory GI play, led by another promotional, wheeler-dealer CEO adept at fueling takeout hype – Bobby "I dare you to short my stock" Alexander -- who similarly stepped in as the savior of a sinking ship after the last one was fired. HRMY's drug – like ABVX -- was developed by a clique of French scientists, led by a quack with a history of questionable scientific conduct. *Plus ça change, plus c'est la même chose*.

"Three months after here is the readout, we are going to run out of cash and we would go bankrupt. …it's like a Hollywood movie. Three days we went from maybe we go bankrupt to you know one of the honestly one of the star [sic] of the NASDAQ. Within three hours we raise $750 million and we had essentially more than $3 billion in demand." – Abivax CEO Marc de Garidel

YouTube interview: *Smooth* Billion Biotech Exits



The 72 Hours that SAVED a biotech from BANKRUPTCY



Source: https://flot.bio/episode/marc-de-garidel-abivax-exit/; https://www.youtube.com/watch?v=KL5GWkFFOiY

The best fraud theses are those that are instantly obvious. The crux of SLNO's problem only took a few minutes to spot – a failed Phase 3, for a 50-year old compound so toxic that it was only used in neonatal intensive care units with concurrent, massive doses of diuretics to prevent catastrophic fluid retention, along with ongoing cardiac monitoring. Sending parents home with an extended-release tablet version was an easy disaster to predict – thus, 8 reported fatalities a year later. For ABVX, the éléphant in the room is instantly visible on the PubChem tables for its drug: if you're shilling a daily, long-term therapy for UC, you really don't want it to share a defining chemical characteristic with a table of regulated/banned pollutants.

PubChem Chemical and Physical Properties table for obefazimod: computed logP and TPSA

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	338.71 g/mol	Computed by PubChem 2.2 (PubChem release 2025.09.15)
XLogP3-AA	5.9	Computed by XLogP3 3.0 (PubChem release 2025.09.15)
Hydrogen Bond Donor Count	1	Computed by Cactvs 3.4.8.24 (PubChem release 2025.09.15)
Hydrogen Bond Acceptor Count	6	Computed by Cactvs 3.4.8.24 (PubChem release 2025.09.15)
Rotatable Bond Count	3	Computed by Cactvs 3.4.8.24 (PubChem release 2025.09.15)
Exact Mass	338.0433751 Da	Computed by PubChem 2.2 (PubChem release 2025.09.15)
Monoisotopic Mass	338.0433751 Da	Computed by PubChem 2.2 (PubChem release 2025.09.15)
Topological Polar Surface Area	34.2 Å²	Computed by Cactvs 3.4.8.24 (PubChem release 2025.09.15)
Heavy Atom Count	23	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	388	Computed by Cactvs 3.4.8.24 (PubChem release 2025.09.15)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2025.09.15)

Stockholm Convention initial "Dirty Dozen" - logP table of pesticides and industrial chemicals

Stockholm Convention on Persistent Organic Pollutants (POPs)

The 12 initial POPs under the Stockholm Convention

Initially, twelve POPs have been recognized as causing adverse effects on humans and the ecosystem and these can be placed in 3 categories:

- **Pesticides**: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene;
- **Industrial chemicals**: hexachlorobenzene, polychlorinated biphenyls (PCBs); and
- **By-products**: hexachlorobenzene; polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), and PCBs.

Original Stockholm POPs: LogP / logKow

Original Stockholm POP	Type	Representative logP / logKow
Aldrin	Pesticide	~6.5
Chlordane	Pesticide mixture	~6.0–6.2
DDT	Pesticide	~6.9
Dieldrin	Pesticide	~6.2
Endrin	Pesticide	~5.3–5.6
Heptachlor	Pesticide	~5.3
Hexachlorobenzene	Pesticide / industrial byproduct	~5.7–6.2
Mirex	Pesticide / flame retardant	~5.3
Toxaphene	Pesticide mixture	~5.9 median; range ~3.3–6.6
PCBs	Industrial chemicals	~4.7–8.2
Dioxins / PCDDs	Industrial byproducts	~6.5–7.7
Furans / PCDFs	Industrial byproducts	~6.5–7.0+

Source: https://pubchem.ncbi.nlm.nih.gov/compound/49846599#section=Depositor-Supplied-Synonyms; https://chm.pops.int/theconvention/thepops/the12initialpops/tabid/296/default.aspx

Obefazimod's purported MOA is a hoax: it is simply a run-of-the-mill, broad-spectrum, lipophilic mass-action drug – similar in class to anti-parasitic and anthelmintic agents, like ivermectin for worms or chroloquinine for malaria – only radically more lipophilic. Thus, ABVX began as an HIV play, re-inventing itself as a COVID cure when fringe, right-wing media started pushing ivermectin, before pivoting to UC. Anthelmintics are literally, pharmacologically targeted poisons for parasites. Predictably, they are only given once or pulse-dosed for a few days – so as not to also poison the host. Prescribing a mass-action lipophile like obefazimod for chronic, daily use in UC would be as reckless as writing ivermectin refills – or, like sending parents home with SLNO's drug, which would make that particular safety debacle look like child's play.

Shanley et al 2024 and Lochman et al 2026, respectively: ABX464 pharmacophore as a "new nematocide" with activity against C. elegans, H. contortus, and other parasitic nematodes

Structure activity relationship and target prediction for ABX464 analogues in *Caenorhabditis elegans*

Biotransformation of obefazimod, a novel potential anthelmintic, in sheep and the target nematode *Haemonchus contortus*

"As the efficacy of current anthelmintic drugs is being compromised by the emergence of drug resistance, a search for novel therapeutics with new modes of action is necessary. Obefazimod (ABX464) originally developed for human inflammatory diseases, has recently shown promising nematocidal activity against Haemonchus contortus and other parasitic nematodes."

Source: https://www.sciencedirect.com/science/article/pii/S0968089623003887; https://www.nature.com/articles/s41598-026-49484-1;

As detailed in later chapters, there is almost no FDA precedent for a small molecule at logP > 6 chronically dosed at high mg. The few that exist are flops or orphan, oncology, or niche/exotic drugs (organ transplant rejection) with boxed warnings, heavy monitoring, high toxicity, or FDA withdrawal.

The thin cohort of FDA-approved, lipophilic small-molecule drugs reads as a liability catalogue -- none is a clean, convenient maintenance therapy. Clofazimine is the textbook tissue-storage drug -- red-brown skin/conjunctival discoloration and crystalline deposition in adipose. The one drug matching obefazimod on logP and dose – acitretin at 25-50mg – has a 4-month terminal half-life due to fat storage and is Pregnancy Category X with a multi-year post-treatment conception ban and a $37MM global market..

High LogP small-molecule drugs dosed daily

Drug	Indication	Dose / day	Boxed warning	Monitoring burden
Acitretin logP ~6.1	Severe plaque psoriasis	**25–50 mg**	Teratogenicity (Preg. Cat. X); hepatotoxicity; alcohol prohibited	Two-form contraception + serial pregnancy tests; no blood donation 3 yrs; LFTs, lipids
Tamoxifen logP ~6.3	Breast cancer (treatment + prevention)	**20 mg**	Endometrial cancer / uterine sarcoma; stroke; pulmonary embolism	Gynecologic exams; thromboembolism watch; periodic CBC
Clofazimine logP ~7.7	Leprosy (orphan); NTM off-label	**50–100 mg**	Not boxed — crystalline GI deposition → bowel obstruction, splenic infarction, death	GI / skin surveillance; skin discoloration near-universal. U.S. expanded-access only since 2004
Avacopan logP ~7.5†	ANCA-associated vasculitis (adjunctive)	**30 mg BID (60 mg)**	Not boxed — hepatotoxicity; FDA 3/2026 alert (fatal DILI, VBDS); withdrawal proposed	Baseline + periodic liver function tests
Cinacalcet logP ~6.1	2° hyperparathyroidism (dialysis); parathyroid-ca hypercalcemia	**30 → 180 mg**	Not boxed — hypocalcemia; seizures	Serum calcium (monthly), phosphorus, iPTH
Raloxifene logP ~6.1	Postmenopausal osteoporosis; breast-cancer risk reduction	**60 mg**	Venous thromboembolism (DVT / PE); death from stroke	Thromboembolism watch; uterine / lipid monitoring
Toremifene logP ~7.2	Metastatic breast cancer	**60 mg**	QT prolongation	ECG, electrolytes (K / Mg), CBC, liver function

Source: logP values are calculated; standardize to one source (e.g., PubChem XLogP3) before publication. All listed drugs are ionizable (acid or base), so log $D_{7.4}$ runs 1–2+ log units below logP. †Avacopan logP to be confirmed. By contrast, obefazimod (logP ≈ 6.34) is permanently neutral across pH 2–12 — log D = logP, no ionization rescue — dosed 25–50 mg once daily.

Avacopan – one of only two neutral + extreme-logP comparators, acquired by Amgen for $4B in 2022 – is a disaster. It sports a rare/exotic indication: ANCA-associated vasculitis, which has a one-year mortality rate of 80% if untreated. In Apr ‘26, the FDA proposed to rescind approval due to liver injury and issues with the trial and NDA. The other comparator was pulled in ’95 – lipophilicity is at the root of their toxicity.

Six of the seven comparators on the previous page are ionizable -- five weak bases and one acid -- meaning their "high logP" overstates how lipophilic they are in plasma; each gets a 1–2+ log-unit ionization rescue and travels as a far less lipophilic charged species. Avacopan is the one exception as it is neutral at physiological pH. The only commercially successful high LogP + neutral molecules we see are CFTR modulators for cystic fibrosis. However, their logP values are 3-5, making obefazimod >10-1000x more lipophilic at 6.34. Moreover, they are reserved for a fatal orphan indication and carry severe boxed warnings for drug-induced liver injury and liver failure, with onerous monitoring requirements.

Neutral (log D = logP) high-logP chronic oral drugs – the very small set

Drug	Ionizable group	Charge at pH 7.4	log $D_{7.4}$ vs logP
NEUTRAL · log D = logP — no ionization rescue			
Obefazimod logP ~6.34	None across pH 2–12 — permanently neutral	**neutral**	**log D = logP**
Avacopan logP ~7.5†	Only a weak arylamine (pKa ~4–5); piperidine N acylated (amide)	**essentially neutral**	**log D ≈ logP**
Probucol logP ~10	Bis-phenol (pKa ~10–11); no basic center	**neutral**	**log D ≈ logP**
IONIZABLE · log D < logP — effective lipophilicity rescued by charge			
Acitretin logP ~6.1	Carboxylic acid (pKa ~4.8)	anion	log D ≪ logP (~−2.6)
Tamoxifen logP ~6.3	Tertiary amine (pKa ~8.8)	cation	log D < logP
Clofazimine logP ~7.7	Imino base (pKa ~8.5)	partial cation	log D < logP
Cinacalcet logP ~6.1	2° aliphatic amine (pKa ~8.5)	cation	log D < logP
Raloxifene logP ~6.1	Piperidine base (pKa ~8–9) + 2 phenols	cation / amphoteric	log D < logP
Toremifene logP ~7.2	Tertiary amine (pKa ~8.8)	cation	log D < logP

Only two neutral, extreme-logP comparators that we see

Obefazimod -- ???

Avacopan -- under threat of FDA withdrawal

Probucal -- withdrawn

The other extreme-logP comparators are ionizable, which means they are less lipophilic than their logP would otherwise indicate

†Avacopan neutrality is structure-based; probucol logP is calculated (~10); acitretin log D reflects near-complete ionization at pH 7.4. logP values are calculated.

Avacopan and obefazimod are both lipophilic, neutral, low TPSA. The FDA's withdrawal effort and journal retractions are typical for this tiny comparator set – a graveyard which violates basic drug rules like Lipinski, 3/75, Rule of Two and is littered with recalls or launch flops like propucal and etrasimod.

Avacopan (TAVNEOS) – recent press and controversy

CDER proposes to withdraw approval of TAVNEOS

NEJM Retracts Pivotal Trial of FDA-Approved Drug

— Move follows actions "inconsistent with proper research conduct," journal says

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Amgen's Tavneos faces withdrawal after FDA probe flags data tampering

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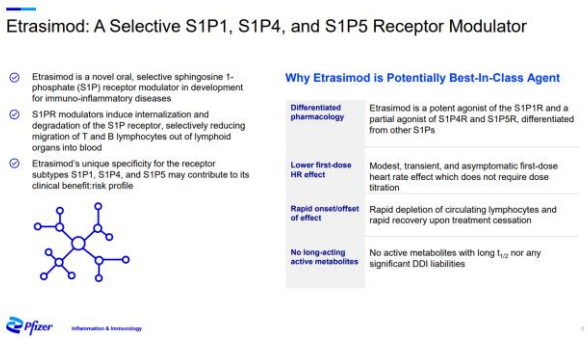
FDA Warns of Serious Liver Injury Risks From Vasculitis Drug Tavneos

Source: https://www.fda.gov/drugs/drug-alerts-and-statements/cder-proposes-withdraw-approval-tavneos; https://www.reuters.com/legal/litigation/medical-journal-retracts-paper-amgens-tavneos-drug-trial-after-fda-findings-2026-06-29/; https://firstwordpharma.com/story/7231776; https://www.webmd.com/drugs/updates/fda-warning-vasculitis-drug-tavneos-serious-liver-injury-risks

The only UC drug we could find with a headline logP anywhere near obefazimod is etrasimod, but the latter's liability is rescued by ionization while obefazimod's is not (see pKa, physical properties chapter). Moreover, etrasimod's 2 mg daily dose is microscopic, while obefazimod's 25/50mg is akin to a horse pill at this logP. Irrespective, etrasimod's recent, colossal UC launch flop is the canary in the coal mine for obefazimod. Pfizer paid $6.7B for Arena in 2021 with $4B peak sales estimates – the asset already appears to be a total writeoff with immaterial sales..

Timeline of Arena/Pfizer UC drug's (etrasimod) rapid failure and write-off

Dec 2021: Pfizer presentation talking up etrasimod as best-in-class



Etrasimod: A Selective S1P1, S1P4, and S1P5 Receptor Modulator

- Etrasimod is a novel oral, selective sphingosine 1-phosphate (S1P) receptor modulator in development for immuno-inflammatory diseases
- S1PR modulators induce internalization and degradation of the S1P receptor, selectively reducing migration of T and B lymphocytes out of lymphoid organs into blood
- Etrasimod's unique specificity for the receptor subtypes S1P1, S1P4, and S1P5 may contribute to its clinical benefit:risk profile

Why Etrasimod is Potentially Best-In-Class Agent

Differentiated pharmacology	Etrasimod is a potent agonist of the S1P1R and a partial agonist of S1P4R and S1P5R, differentiated from other S1Ps
Lower first-dose HR effect	Modest, transient, and asymptomatic first-dose heart rate effect which does not require dose titration
Rapid onset/offset of effect	Rapid depletion of circulating lymphocytes and rapid recovery upon treatment cessation
No long-acting active metabolites	No active metabolites with long $t_{1/2}$ nor any significant DDI liabilities

Pfizer Inflammation & Immunology

Oct 2023: FDA approval

FDA Approves Pfizer's Ulcerative Colitis Drug, $6.7B Arena Buy Pays Off

Jan 2024: First impairment charge

Pfizer Takes Impairment Charges On Velsipity And Prevnar 13

As we are increasingly focused on prioritizing our investments to drive forward-looking growth, our GAAP results include a $1.4 billion intangible asset impairment charge associated with etrasimod, based on a change in development plans for additional indications and overall revenue expectations, but I will point out

Feb 2026: Total write-off? PFE earnings call.

In support of our goal to enhance R&D productivity and focus on high-impact medicines, our fourth quarter GAAP results reflect strategic decisions in our development plans and **updated long-range revenue forecast for certain products** and pipeline assets. As a result, we recorded approximately **$4.4 billion of noncash intangible asset impairments** related to several medicines…

Source: https://s206.q4cdn.com/795948973/files/doc_presentation/2021/12/13/Final-II-Investor-Day-Triad_2-Presentation.pdf; https://s206.q4cdn.com/795948973/files/doc_financials/2023/q4/Q4-2023-Earnings-Conference-Call-Prepared-Remarks-FINAL.pdf; https://insights.citeline.com/SC149711/Pfizer-Takes-Impairment-Charges-On-Velsipity-And-Prevnar-13/

Thus, two recent big pharma acquisition flops involve high-logP drugs – a third buyer is unlikely to be as dumb. Amgen blew $4B for Chemocentryx's avocopan; Pfizer torched $7B on Arena's UC drug etrasimod – a rapid launch flop and impairment -- with similar logP + TPSA profile as ABX464.

Avacopan/Chemocentryx and Esrasimod/Arena Pharmaceuticals – acquisitions and drug issues

"(Etrasimod) has the potential to be best-in-class drug in these indications...could be a multi-billion blockbuster drug in just Crohn's and ulcerative colitis and we forecast risk adjusted revenue of $3.8 billion…"

ChemoCentryx Data Fraud Allegations Surface

Updated: FDA claims trial 'manipulation' tainted approval of ChemoCentryx drug now owned by Amgen

Controversial drug at center of multibillion-dollar Amgen deal faces more questions after paper retracted

Pfizer bets on Arena's promising bowel disease treatment in $6.7 bln deal

"(Etrasimod) has the potential to be best-in-class drug in these indications...could be a multi-billion blockbuster drug in just Crohn's and ulcerative colitis and we forecast risk adjusted revenue of $3.8 billion."

Pfizer Takes Impairment Charges On Velsipity And Prevnar 13

Source: https://www.bizjournals.com/sanfrancisco/news/2026/07/01/amgen-drug-deaths-vasculitis-tavneos-chemocentryx.html; https://www.startuphub.ai/ai-news/technology/2026/chemocentryx-data-fraud-allegations-surface; https://endpoints.news/fda-claims-trial-manipulation-tainted-approval-of-chemocentryx-drug/; https://insights.citeline.com/SC149711/Pfizer-Takes-Impairment-Charges-On-Velsipity-And-Prevnar-13/; https://www.reuters.com/markets/deals/pfizer-acquire-arena-pharmaceuticals-67-bln-deal-2021-12-13/

ABVX CEO Marc de Garidel was hired in 2023 after the last CEO was bounced. A former ABVX C-level executive told us that "Marc was brought in just to do a [quick flip]…he didn't think he would be here this long…I'm confident he thought he was going be within 12 months"; "they never thought they were going to have to take it this far…they had no idea what they were doing…we kind of used to laugh…craziest place I had ever worked…it wasn't really a functioning company…they thought they were going to sell, and they didn't have anybody that wanted to buy it."

Abivax allegedly couldn't find a buyer; "craziest place I ever worked"

A: "I think they thought that they would have sold this company by 2022. ***They never thought they were going to have to take it this far****…they had no interest in going into the US, building relationships in the US, doing a clinical trial in the US…I don't think they had the capabilities…the impression is sort of,* ***they had no idea what they were doing*** *because they never wanted to do it. They never wanted to have to do a Phase 3 trial in the States…that's not what they were trying to do. They were trying to do an HIV product or get some data and sell the company five years ago…****we kind of used to laugh. It was like this is the craziest place I had ever worked. It wasn't really a functioning company."***

Q: "When you say it wasn't a functioning company, what do you mean? They just wanted to flip it after Phase 2? Just package it, dump it?"

A: "Yeah, exactly. ***They thought they were going to sell, and they didn't have anybody that wanted to buy it."*** *– Ex-Abivax executive*

ABVX allegedly aimed for a quick flip

*"****Marc was brought in to just do [a quick flip].*** *He didn't think that he would be here this long. I'm confident* ***he thought he was going to be within 12 months****, and frankly, I'm surprised that they haven't sold yet. I'm also shocked at the valuation of the company. Honestly."– Ex-Abivax senior executive*

Source: Scorpion Capital consultation calls with experts

The ex-ABVX executive continued: "they've been trying to sell this thing for years" -- "everybody passed on it…30 different companies that they were trying to sell this out to." He dismissed speculation of the obvious French suitor -- "I know for a fact Sanofi wasn't really interested" -- and cited skepticism of the purported mechanism and abrupt pivot: "it's not an elegant story…this was an HIV drug…it's not an easy story to tell."

Sanofi allegedly not interested; buyers passed on the company; "not an elegant story"

A: "I think that if positioned, and they sell it to a big company with a portfolio in IBD, they could position this appropriately for the right patient, and they would price it, and they would market the hell out of it. Like an AbbVie would have killed this. They would crush it. They have the expertise. They have the marketing kind of chops, and they have the relationships in IBD. That's why there's only a handful of companies that could do really well with this. ***I know for a fact Sanofi wasn't really interested in it. You'd think there'd be some French connection, but there wasn't."***

Q: "What do you mean Sanofi wasn't interested in it?"

A: "There were just conversations. ***They've been trying to sell this thing for years****. As part of diligence, some companies believed in it, some other companies didn't believe in it. They wanted to wait and wait and see for the data."*

Q: "These are stale conversations, long before Phase 3 data?"

*A: "Yeah, over time…****everybody passed on it. I think they had 30 different companies that they were trying to sell this out to. I think everybody passed on it originally****. And now I think there's only a handful that are really interested in paying the premium for it. So it went from 30 companies. Now there are probably 5 or 6 that are truly viable."*

Q: "Who do you think would not be interested? What did you hear about Sanofi's interest?"

A: "I just think it was you ***either believe in the mechanism of action, or you don't****. Even if you talk to the KOL community, it's the same. It's* ***not an elegant story****. For example, like Entyvio. It's gut selective. There's an elegant way of saying, hey, this is purposely designed for the GI tract.* ***This was an HIV drug. It's not an easy story to tell."***

Q: "And so Sanofi didn't believe in the mechanism of action; is what you're saying?"

A: "Correct…this was years ago." – Ex-Abivax senior executive

Source: Scorpion Capital consultation calls with experts

The ex-C level executive indicated that the lack of dose response "was the number one big red flag for the asset in total…in this market, every other product has a dose response…you have to believe that this just mechanistically different without a dose-response…they just couldn't get their head around it." We note that the FDA is permissive of an unclear MOA with a clear dose-response, or absent dose-response with a clear MOA – but not both, and scrutinizes such NDA's much more aggressively.

Potential acquirers were skeptical of lack of dose response

*A: "Yeah, and **it was the dose. There were no differences**, at least in the Phase 2 study, in terms of the **dose effect was not profound."***

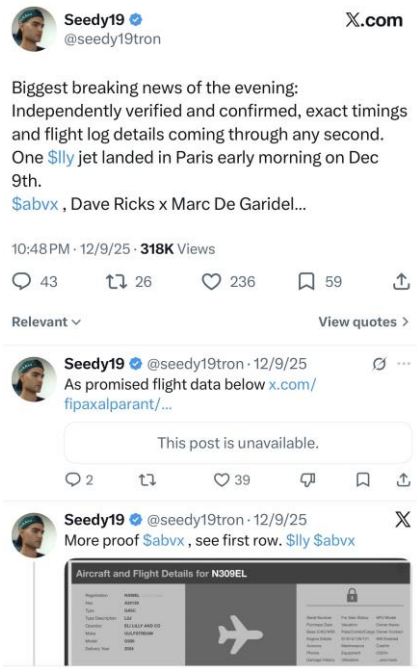
Q: "There's no dose-response with the drug. That's very clear looking at it."

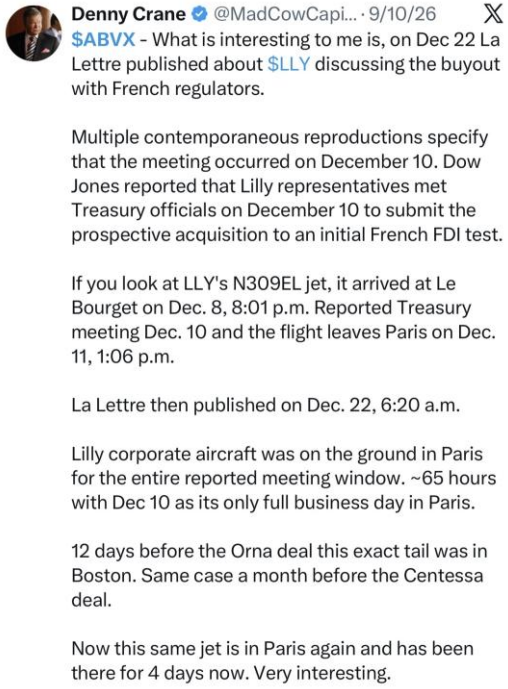
*A: "Exactly, exactly. **That was the number-one big red flag for the asset in total. Because in this market, every other product has a dose-response. And this one's unique. So you have to believe that this is just mechanistically different without a dose-response**. The questions were on the mechanism of action, not believing it or dose-response, and KOLs depending on the questions and the companies. It's like **they just couldn't get their head around it. So then they didn't believe it**. So then the conversations in BD ended, or obviously, some of the KOL conversations; no matter what they did, they just couldn't get — yeah, I'm just skeptical. **Not everyone in the IBD community believes in it."** – Ex-Abivax senior executive*

Source: Scorpion Capital consultation calls with experts

Bagholders praying for an acquisition appear to be in the bargaining stage of grief, and are simply not reading the room. We get the sense Big Pharma CEO's think ABVX is a joke – we assume their corp dev teams have been hounded by its bankers for years. The relentless media blitz, social media hype, and buyout rumors planted in the French press are typical of a weak hand. Eli Lilly's CEO has recently become active on X, with a recent post mocking those who track corporate jets for clues to M&A activity – an apparent shot at ABVX fanboys tracking every Lilly plane landing in Paris.

Eli Lilly CEO's post on X; other posts tracking alleged Eli Lilly private jet movements







Source: Scorpion Capital consultation calls with experts

AbbVie has been particularly vocal at multiple investor events, with their Chief Scientific Officer making scathing remarks about obefazimod's "potential cardiovascular or teratogenic issues" -- "this aggressiveness in contraception, whether it's for females and males…even males are told to continue contraception for 6 months after they finished the study"; "suggests that this is teratogenic…then this elevated miR-124 elevated levels…quite a bit of literature that is associated with cardiac dysfunction, particularly heart failure risk"; "based on their endpoints that they've published and protocols, they're looking at echocardiograms and I guess, careful assessments of EKGs."

AbbVie EVP R&D/Chief Scientific officer – Piper Sandler conference, Dec 3 2025, excerpts:

"I guess the questions that would remain on this type of agent is what does that mean long-term safety and where could something like that eventually fit in. We don't see the efficacy differentiating as of yet with induction data. We'll have to wait for maintenance…but when you look at the safety profile, Skyrizi and Rinvoq don't lead to ***headaches****…we also haven't seen* ***pancreatic enzyme elevations*** *with Skyrizi or Rinvoq, whereas in induction data, I think with this agent, there has been elevations…we did not have* ***this aggressiveness in contraception, whether it's for females and males is what we've observed in their clinical trials where even males are told to continue contraception for 6 months after they finished the study and to maybe even avoid the study*** *if they have a partner that's of child-bearing potential that is considering having children…along with what's publicly available in* ***their own protocols that suggests that this is teratogenic****. So that will be something else that will come out over time. And then* ***this MIR-124 elevated levels, there's quite a bit of literature that is associated with cardiac dysfunction, particularly heart failure risk****. And I believe they're -- based on their endpoints that* ***they've published and protocols, they're looking at echocardiograms and I guess, careful assessments of EKGs****. So all of that taken together, one will have to see. But right now, today, what we have in front of us with Phase III tested induction and maintenance with Skyrizi and Rinvoq we don't have those issues, and we have very strong efficacy. And then the combos that we would bring wouldn't have these* ***potential cardiovascular or teratogenic issues****."– Roopal Thakkar, AbbVie EVP R&D and Chief Scientific Officer*

Source: Scorpion Capital consultation calls with experts

Unsurprisingly given the field's skepticism, the pivotal phase 3 trial was delayed for years and failed to enroll due to lack of physician interest. Two of our most reliable indicators for biotech scams are a lack of independent validation and scientific interest from reputable researchers/institutions + trial enrollment delays. ABVX is an extreme match on all counts. Its Phase 3 trial began enrolling in 2022, but by 2023/24 – per every ex-employee we interviewed – the trial was floundering, unable to attract physicians and patients: "they had almost no sites open…a lot of delays…they couldn't get people in the US…so they [had] a big amount of trial sites in Poland and Ukraine…in the middle of a war…you can't rely on that."

"until September 2023, they had almost no sites open"

*"If you go on clinicaltrial.gov, you will see Phase 3 started a couple of years before, but **until September 2023, they had almost no sites open. A lot of delays**. I think at that time there were 100 patients involved…I can tell you that me and my team came in to drive enrollment and to get the things started because they were in delays. **Not a lot of sites were open** at that time…we had a lot of sites, especially in the US, that **did not enroll at all**.. if we did it across the US, **we didn't have sites with 10-plus registrations. It was more like we're getting 1 to 2 patients**. I would have to go back and look at the numbers." – Ex-Abivax senior MSL role, via Amplity*

Abivax couldn't get many enrolled in the US so focused on low quality sites in Poland, Ukraine, etc.; issues with sites during war

***"They couldn't get people in the US. So they did have a big amount of trial sites in Poland and Ukraine**. And that was also around the time when conflict in Ukraine was happening. And there was a lot of discussion, well, if a lot of your trial sites are in Ukraine and they're in the **middle of a war and being invaded, you can't rely on that**. People like Sheldon, when he came on, and other people were trying to encourage leadership, like you need to focus in the US, you need to ramp up in other areas. That was a big point of contention and debate to try to get them to see the bigger picture a little bit." – Ex-Abivax executive*

Source: Scorpion Capital consultation calls with experts

Biotech stories of the too-good-to-be-true variety tend to exhibit another pattern – an overnight transformation of their stock and fortunes, right when they were on the brink. A flailing company with its back against the wall has the incentives -- and levers -- to conjure whatever data it takes. Pay-to-play CRO's, trial sites, and investigators top the list, especially offshore. Ex-employees told us that US KOL's were skeptical and confused by ABVX's claims, forcing the trial toward low-quality countries – "they were looking at any country…we struggled heavily in the US…concern that we would even have enough patients to justify getting a US label." The "top-tier, top-10 KOLs…they saw the data…they all had questions…they were definitely skeptical because it was an unproven mechanism…we struggled in the community"; "they were confused by it…people didn't get it…."

Trial was struggling; physicians were skeptical

*A: "The honest answer is **they were looking at any country**. India was debated….**we struggled heavily in the US**. I haven't seen the actual numbers of the n of patients in the US, but it was very difficult for us to be able to, despite having a number of sites open, to actually have patients. I think there was **a concern that we would even have enough patients to justify getting a US label**."*

Q: "Why do they have such a hard time with people in the US?"

A: "Because there's so many available agents in the US." […]

Q: "So, how do you interpret that lack of US enthusiasm and the difficulties that they had?"

*A: "I think **they were confused by it**. There was concern about the dose-ranging component of it. I think they were confused about the origin of the molecule. Obviously, it was developed again, for HIV…the **mechanism of action is confusing**…it's new. It's different…up-regulator, you insert word. It was difficult, and **people didn't get it,"** – Ex-Abivax senior executive*

Trial was struggling

*"[KOL names redacted], those folks, **top-tier, top-10 KOLs. They saw the data. They all had questions on it.** But what we tried to do was get their buy-in, get their input as part of the steering committee… but **generally, it was mixed…they were definitely skeptical because it was an unproven mechanism in the space…We struggled in the community."** – Ex-Abivax senior executive*

Source: Scorpion Capital consultation calls with experts

China appears to be a key pillar of Abivax phase 3 ABTECT clinical data – a major red flag. Country-level enrollment remains hidden, but regional figures indicate North America P3 enrollment was a mere 10% of total while Asia was 24%, with ~50 Chinese sites listed in the ClinicalTrials.gov record, second only to the US in terms of the number of total sites shown.

ABVX press release Apr 29. 2025 – regional enrollment figures for Phase 2b and Phase 3

Trial Participant Baseline Characteristics: ABTECT Phase 3 vs. Obefazimod Phase 2b

	ABTECT Phase 3	Phase 2b
Study Participants	1,275	252
Baseline MMS (7-9)	65%	71%
Prior Advanced Therapy Failure	48%	48%
Corticosteroids	42%	52%
Geographic Distribution	North America : 10% Western / Central Europe: 22% Eastern Europe:38% Asia:24% ROW: 6%	North America : 1% Western/Central Europe: 33% Eastern Europe: 66%

ABTECT Phase 3	Phase 2b
North America : 10% Western / Central Europe: 22% Eastern Europe:38% Asia:24% ROW: 6%	North America : 1% Western/Central Europe: 33% Eastern Europe: 66%

Source: https://ir.abivax.com/news-releases/news-release-details/abivax-announces-completion-enrollment-phase-3-abtect-trials

The Chinese sites listed include numerous problematic military facilities -- such as the PLA 900th Hospital – consistently identified as hubs for coercive organ sourcing and transplant tourism. At least five sites have been implicated in executed-prisoner organ sourcing; others allegedly took bribes from drug reps, falsified data, or engaged in other dubious practices.

A few examples of problematic Chinese sites listed in ABTECT ClinicalTrials.gov record; various military hospital trial sites discussed for dubious organ/medical practices per sources below

Guangzhou, Guangdong, China, 510515
Nanfang Hospital of Southern Medical University

Yuexiu, Guangdong, China, 510080
The First Affiliated Hospital of Sun Yat-sen University

Shanghai, Shanghai Municipality, China, 200127
Renji Hospital Shanghai Jiaotong University School of Medicine - West Branch

Changsha, Hu'nan, China, 410011
The 2nd Xiangya Hospital of Central South University

China forcefully harvests organs from detainees, tribunal concludes

Doctor jailed for 17 years over bribery, unnecessary operations

Organ Procurement and Extrajudicial Execution in China: A Review of the Evidence

*"The **military-medical complex became heavily involved in transplant activity** and research; the state began subsidizing a nascent immunosuppressant industry. Transplant waiting times went from many months to just weeks, days, and sometimes hours"*

Source: https://global.chinadaily.com.cn/a/202411/01/WS67242a32a310f1265a1cacb1.html; https://global.chinadaily.com.cn/a/202411/01/WS67242a32a310f1265a1cacb1.html; https://www.nbcnews.com/news/world/china-forcefully-harvests-organs-detainees-tribunal-concludes-n1018646; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3598791; https://www.upholdjustice.org/node/636

Chinese trials are the target of recent Congressional scrutiny. A Jun 2026 letter targeted Pfizer's use of trial data from military hospitals, highlighting suspiciously rapid enrollment, "lack of ethical safeguards" for "informed consent and voluntary participation," and "undue influence" and "overstating efficacy" – noting that Pfizer will halt trials at PRC facilities.

Jun 2026 Congressional letter to Pfizer CEO; other press on Chinese

US clinical trials in China questioned by US lawmakers

US House committee opens investigation into Merck, AbbVie China drug trials

Pfizer Conducted Clinical Trials at Chinese Military Hospitals

JUNE 30, 2026

Select Committee Launches Investigation Into Pfizer's China Work

Chairman John Moolenaar of the Select Committee on China has sent a letter to Pfizer Chief Executive Officer Dr. Albert Bourla asking the pharmaceutical company to provide more information about the company's clinical drug trials in China. Publicly available information on **ClinicalTrials.Gov** already shows the company has developed drugs in clinical trials at Chinese military hospitals, and in Xinjiang, China, where the Chinese Communist Party (CCP) is conducting a genocide of Uyghur Muslims and other minorities.

Source: https://files.constantcontact.com/f0eecb46901/7ce2c65d-4e4f-4c62-81c5-2560781cacbd.pdf; https://chinaselectcommittee.house.gov/media/letters/pfizer-conducted-clinical-trials-at-chinese-military-hospitals; https://www.reuters.com/business/healthcare-pharmaceuticals/us-clinical-trials-china-questioned-by-us-lawmakers-2024-08-20/

The Chinese Food and Drug Administration (CFDA) has flagged systemic fraud and corruption in clinical trials, analyzing 1,622 studies: "most of the data in the studies examined was either incomplete, did not meet the agency's analysis requirements, could not be traced or simply concealed negative results."

Credibility of Chinese clinical trials – various articles

Falsified data in 80% of Chinese clinical trials

A Chinese government investigation has revealed that more than 80 percent of the clinical data used to support trials of new drugs in the past year has been fabricated. According to the report, the results of which were cited by the state-owned China News, the authorities have reviewed 1622 clinical trials awaiting market approval, and it turns out that most of the data in the studies examined was either incomplete, did not meet the agency's analysis requirements, could not be traced or simply concealed negative results. However, this comes as no news to the CFDA, whose top manager already called the

Note To The Chinese FDA: When 80% Of Your Data Is Bad, How Trustworthy Is The Other 20%?

China cracks down on fake data in drug trials

Can we trust clinical trials from China?

Retractions, paper mills, and misconduct, oh my

Source: https://www.pulmccm.org/p/can-we-trust-clinical-trials-from; https://biostock.se/en/2016/10/forfalskade-data-i-80-av-kinesiska-kliniska-provningar/; https://pubmed.ncbi.nlm.nih.gov/28516939/; https://www.forbes.com/sites/benjaminshobert/2016/10/11/note-to-the-cfda-when-80-of-your-data-is-bad-how-trustworthy-is-the-other-20/

Predictably, ABVX sites are plagued by exactly these scandals. At least 7 ABTECT-listed sites rank among university hospitals with the most retracted papers in China. Two Chinese ABTECT sites were the top offenders in the entire country with 48 and 31 retractions each – others each had dozens -- per a 2023 study of retractions across 237 centers. One is Nanfang Hospital, known for historic executed-prisoner organ sourcing.

China medical integrity study – various ABTECT sites listed

Research misconduct in hospitals is spreading: A bibliometric analysis of retracted papers from Chinese university-affiliated hospitals

ABTECT Chinese site	Finding from research integrity summary
Nanfang Hospital, Southern Medical University	**ABTECT contact Side Liu** co-authored a retracted GI/cancer paper. Editors identified multiple apparent image overlaps and concluded the reported data were "unreliable."
Xiangya Hospital, Central South University	**48 retracted papers — highest among 237 Chinese university-affiliated hospitals studied.**
First Hospital of Jilin University	**31 retractions — second-highest** among the 237 hospitals studied.
Shengjing Hospital, China Medical University	24 retractions — all 24 classified as **fake-peer-review cases.**
First Affiliated Hospital of Zhengzhou University	24 retractions — the study identified **data manipulation** as a recurring reason, including 5 cases.
Qilu Hospital, Shandong University	23 retracted papers.
Affiliated Hospital of Qingdao University	16 retractions.

Source: https://www.degruyterbrill.com/document/doi/10.2478/jdis-2023-0022/html?utm_source=chatgpt.com; ClinicalTrials.gov ; Nanfang Hospital organ sourcing, p4 https://www.justice.gov/sites/default/files/eoir/legacy/2013/06/14/china_0894.pdf

ABTECT-listed China sites are a cluster of the worst data integrity and fraud issues in the country – the institutional overlap raises grave doubts about ABVX's entire China dataset. One named ABTECT site investigator/contact, also at Nanfang Hospital, is even the author on a retracted GI paper – an MiR paper, no less -- where editors stated the data is unreliable. He ghosted the journal when contacted.

ABTECT-listed China investigator -- ClinicalTrials.gov record + retraction notice

- **Guangzhou, Guangdong, China, 510515**

  Status: **Recruiting**

  Facility: Nanfang Hospital of Southern Medical University

  Contact:
  - Contact
    - Side Liu, MD

Original paper says the study was "designed and conceived by Jide Wang, Aimin Li and Side Liu"

Cellular Oncology (2023) 46:237
https://doi.org/10.1007/s13402-022-00768-4

RETRACTION NOTE

Retraction Note: The POU2F1/miR-4490/USP22 axis regulates cell proliferation and metastasis in gastric cancer

Yizhi Xiao[1] · Side Liu[1,2] · Jiaying Li[1] · Weiyu Dai[1] · Weimei Tang[1] · Li Xiang[2] · Wenjing Zhang[3] · Jianjiao Lin[1,2] · Jing Wang[1] · Xiaosheng Wu[1] · Guangnan Liu[1] · Yuyang Liu[4] · Yaying Chen[5] · Huiqiong Zhu[1] · Yusi Wang[1] · Zhizhao Lin[1] · Qiong Yang[1,6] · Tianming Chen[1] · Yong Sun[1] · Aimin Li[1] · Jing Xiong[1] · Jide Wang[1,2]

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Retraction Note: Cellular Oncology (2020) 43:1017–1033
https://doi.org/10.1007/s13402-020-00553-1

The Editors-in-chief have retracted this article because after publication concerns have been raised regarding a number of figures, specifically:

- Figure 3a: the 24h panels for m-NC and i-NC appear to be identical.
- Figure 4f: the AGS and BGC-823 panels for miR-4490/USP22 appear to partially overlap.

The Editors-in-Chief therefore consider the data reported in this the article to be unreliable.

Jide Wang does not agree to this retraction. The editor was not able to obtain a current email address for Tianming Chen. None of the other authors have responded to any correspondence regarding this retraction.

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Source: https://clinicaltrials.gov/study/NCT05507203?a=9&tab=history&utm_source=chatgpt.com; https://link.springer.com/article/10.1007/s13402-022-00768 4?utm_source=chatgpt.com

Despite ~50 China sites listed on ClinicalTrials.gov, every ex-employee we interviewed, including those who played senior roles in the Phase 3 trials, indicated they were shut out of China with no involvement or visibility -- despite being involved in Japan and South Korea: "we did have sites in China…this is something even my team had no visibility…that was a big black hole for me…they just told me it's operating differently…they didn't need me or my team there…"

Senior individuals involving in trial oversight had no visibility/oversight of China sites

*A: **"We did have sites in China. But this is something my team had no visibility or not even visibility as to how many** — yeah, we do have sites in China and as to how many they enroll because even the CRO was not so involved there, so **that was a big black hole for me**. I don't know what happened with them."*

Q: "Did you guys try to get visibility? So even your team had visibility into everything but China? Didn't you think that was weird?"

*A: "It was. Again, when you're a contractor, you also have to think about what you want to ask for. But China, no, it didn't seem weird to me because **they just told me it's operating differently. They didn't need me or my team there."***

Q: "And was your team involved in South Korea and Japan?"

A: "Yeah, we had the Japanese."

*Q: "You were **involved in South Korea and Japan, but not in China?"***

A: "Yeah." – Ex-Abivax senior MSL role, via Amplity

Source: Scorpion Capital consultation calls with experts

Ex-ABVX employees were shocked when we asked about China sites, given their roles across international sites including those in Asia. They indicated that functional teams involved in basic site evaluation and investigational visits had no involvement in China – "blowing my mind right now"; "I didn't even know that Chinese sites were on the list because we did no work with them whatsoever…no investigational visits, no PI education, nothing"; "I literally had no clue there was anything going on in China…I never had a single meeting with anybody from regulatory, clin-dev, safety, CMO-level, C-level – any of these guys about anything China-related…did not get brought up in any of the work that I was going the entire time…"

China sites were a black hole – "no investigational visits, no PI education, nothing"

"I had no interaction with any Chinese sites whatsoever…I did not work with any Chinese sites at all. It was purely the US, EU, UK, some parts of South Korea, and some parts of Japan…I honestly don't know anything about the China sites at all…I was involved in all of Europe. The entire EU, the US, and then South Korea as well. ***I didn't even know that Chinese sites were on the list because we did no work with them whatsoever. I didn't have any interaction with our regulatory, clin-dev — any teams regarding anything related to China when I was there at all. No startup, no insight, no investigational visits, no PI education, nothing****." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff expressed surprise/bewilderment that Chinese sites listed on ClincalTrials.gov

*"The fact that you're telling me that right now is very surprising because if you had told me that we had five sites in China, I would have been surprised because, again, I didn't do any work with anything China-related the entire time I was there… I was in Japan. I was involved in Japan…****I literally had no clue there was anything going on in China while I was there. I had no idea. I never had a single meeting with anybody from regulatory, clin-dev, safety, CMO-level, C-level — any of these guys about anything China-related****. The name of that* ***country did not get brought up in any of the work that I was doing the entire time I was there****…the fact that you're telling me there's 50 China sites on clinicaltrials.gov is* ***blowing my mind right now****." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

Ex-employees stated that China "was not even on my radar…I didn't even know we had trial sites in China…I never received any data from any of those sites…we never had an SIV [site investigational visit]…this is brand-new information…I had no clue….I worked directly with [C-level executive]…and we never had a single – I'll put it like this: the country China was never brought up in any discussions that I had with anybody at any level…we never discussed anything related to China"; "very, very basic due diligence…we didn't do anything with China at all."

International MSL involved with other countries including in Asia was surprised that Chinese sites listed

A: "…[the] medical team was an international team. In terms of the overall team, we had about 10 people overall, but located in Brazil, Mexico, the EU, North America, Korea, Japan — you name it. We were all over the world."

Q: "Were you involved with China as well?"

*A: **"China? I do not believe we had a medical science liaison there."** – Ex-Abivax international MSL, via Amplity*

Key safety staff state they were in the dark China data

***"It was not even on my radar**. That's why I'm saying. **I didn't even know that we had trial sites in China. I never received any data from any of those sites. We never had an SIV**. We didn't even talk to a CRO about monitoring in China. This is **brand-new information**. I had no clue." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff indicated China was never mentioned in any meetings with senior leadership

*"I had literally no idea there were 50 Chinese…this is **brand-new information you're telling me…I worked directly with [redacted – C-level officer/VP]. And we never had a single — I'll put it like this: the country China was never brought up in any discussions that I had with anybody at any level…we never discussed anything related to China**, whether it be clinical trial strategy, monitoring, safety databases, or anything. I did not interact with anybody regarding China at all." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff state no involvement in site investigation visits

*"A site investigation visit. It's basically to figure out whether a site is capable of running the trial, like the **very, very basic due diligence** that's run in a clinical trial; you do the investigational visit. You make sure that they have all the proper whatever it may be, whether it's like the proper infusion center, the proper pharmacy to dispense the medication, the proper storage — any of that. **We didn't do anything with China at all."** – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

US site quality is the most suspect we've seen at $7B cap – offshore sites look far worse. The lack of tier-1 centers and "real" academic investigators is telling, with heavy reliance on private practices in poorer states and tiny towns – we question their competence/training, trial protocol adherence, data integrity, and endoscopic, safety, and monitoring/reporting standards. Sites below are each roughly an hour from Huntsville, AL and Tampa, FL.

ABTECT trial sites listed on ClinicalTrials.gov – Lakeview Clinical Research (Guntersville, AL), town of 8,500 people; Advanced Research Institute (New Port Richey, FL)







Source: Images from Google Maps after looking up trial sites on ClinicalTrials.gov

Many sites have vague, dubious names and look like sketch "CRO's" in low-income areas – lots of strip malls, no websites we can locate, stock or AI-generated images. Sanchez Clinical Research is typical -- in a derelict Miami strip mall next to a pawn shop with Spanish signage -- yet lists numerous trials and calls itself a fast-growing "Miami research center leader."

ABTECT sites listed on ClinicalTrials.gov – Sanchez Clinical Research (Miami, FL)







Source: Google Maps images; ClinicalTrials.gov; https://sanchezmr.com/departments

The ABTECT foreign sites are troubling. Searches on individual centers listed reveal endless red flags, scandals, and misconduct. A tertiary Mumbai hospital, King Edward Memorial, is typical – patients littered on floors, and a published study that documented recurring informed consent violations at the site, "investigators" who don't understand trial protocols, improper adverse event monitoring, protocol deviations, etc.

ABTECT sites on ClinicalTrials.gov – King Edward Memorial Hospital, Mumbai, India; clinical trial lapses documented in Indian Journal of Medical Ethics, https://doi.org/10.20529/IJME.2019.042





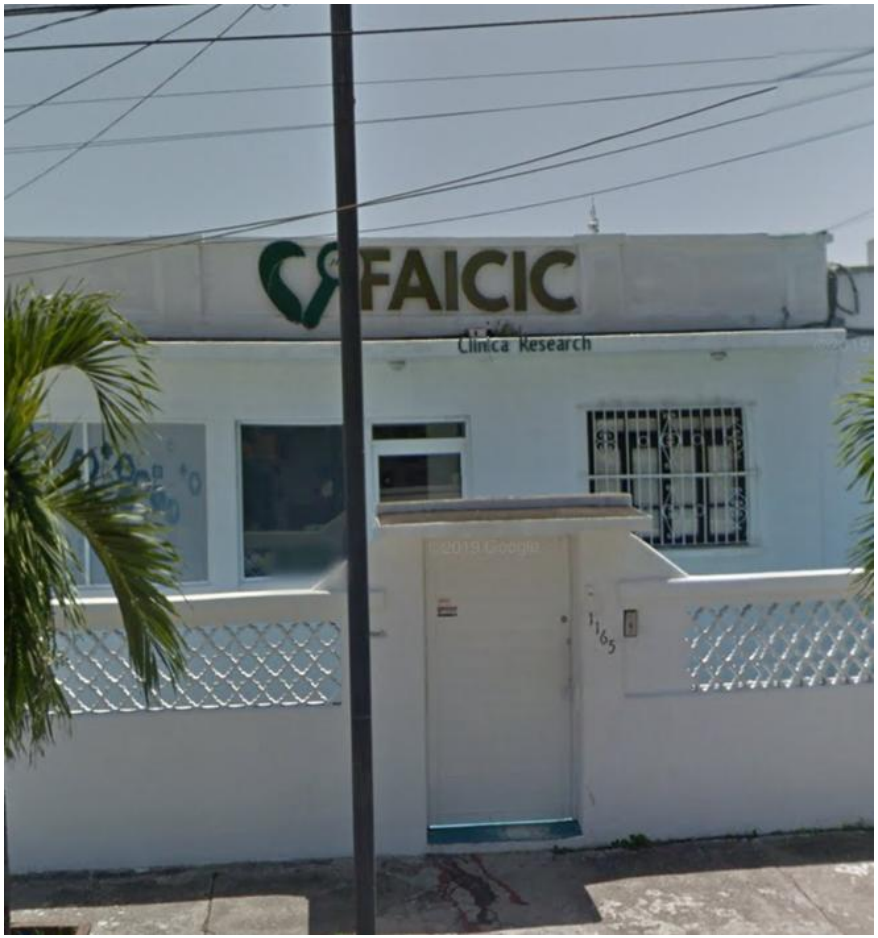




Source: ABTECT trial sites shown on ClinicalTrials.gov; https://doi.org/10.20529/IJME.2019.042; images from Google Maps record for KEM Hospital, Mumbai, India

The Mexico trial sites listed look as preposterous as the India ones. We see no facilities in tier-1 metros like Mexico City – the ones listed are in remote, peripheral areas like Veracruz, 250 miles away; Iraputo; and Monterrey. The FAICIC clinical site in Veracruz is shown below.

ABTECT sites on ClinicalTrials.gov -- FAICIC S. de R.L. de C.V. in Veracruz, Mexico

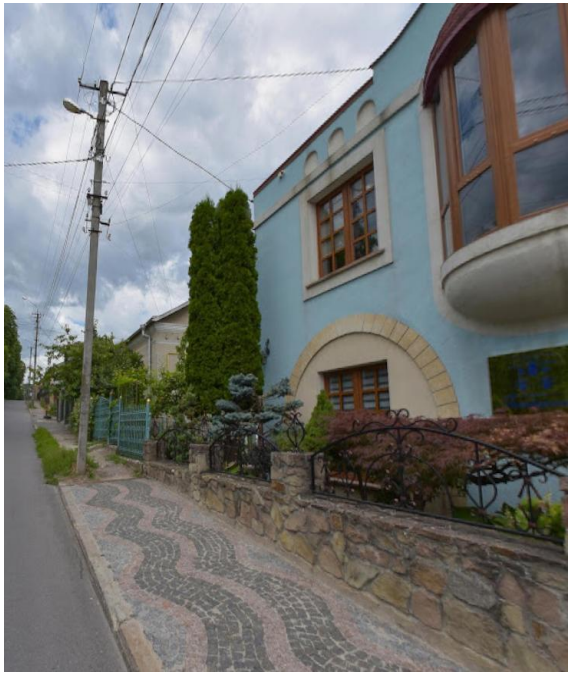




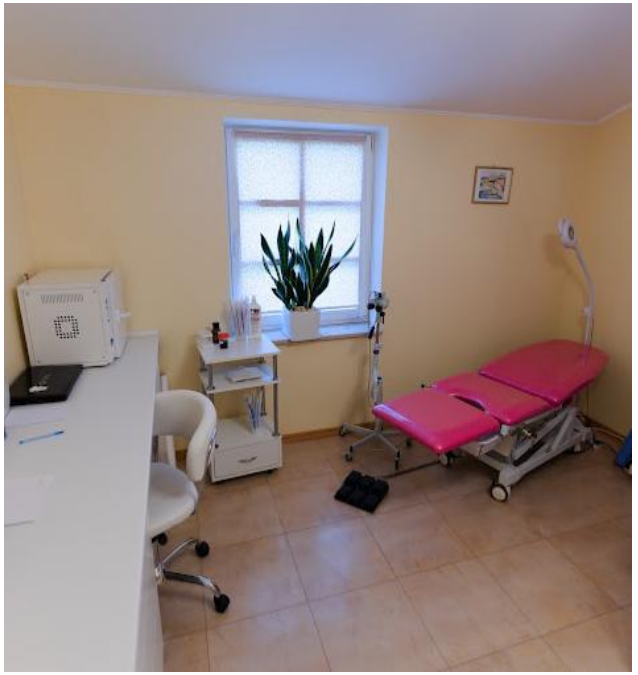
Source: ClinicalTrials.gov, Google Maps images

We count 15 sites listed in Ukraine – enrolling during a war. A recent study noted a collapse in clinical trial reliability since the war began. FDA/EMA precedent doesn't appear to be in ABVX's favor. The FDA recommended excluding Ukraine patients in a recent GI phase 3 trial, and the EMA has warned that wartime data may be unsuitable for regulatory reliance.

ABTECT sites on ClinicalTrials.gov – Ukraine; EMA guidance on Ukraine wartime data







Impact of the war in Ukraine on methodological aspects of ongoing clinical trials - Scientific guideline

Source: ClinicalTrials.gov; Google Maps images -LLC Medical Center The Clinic of Hospodarskyy, Ukraine; NDA indicating negative Ukraine war impact https://cdn.clinicaltrials.gov/large-docs/30/NCT03926130/SAP_002.pdf?utm_source=chatgpt.com; https://www.ema.europa.eu/en/impact-war-ukraine-methodological-aspects-ongoing-clinical-trials-scientific-guideline

Chapter 2. Abivax’s origin story

Abivax claims that ABX464 -- now known as obefazimod – selectively binds to the cap-binding complex (CBC) to increase production of microRNA-124 (miR124). The purported mechanism of action is a moving target. ABVX initially claimed it was a breakthrough antiviral and potential cure for HIV.

The company claimed that ABX464 acted as a specific inhibitor of the viral protein Rev, which is essential for exporting unspliced HIV RNA out of the host cell nucleus. By blocking Rev, the drug supposedly forced abnormal viral RNA splicing, prevented viral replication, and -- crucially -- targeted the latent "HIV reservoir." This mechanism was backed by tiny, open-label Phase 2a trials involving minuscule patient cohorts (initially 26 patients across studies like ABX464-004 and ABX464-005). Abivax publicized these trials as the first-ever demonstration of a statistically significant reduction in the HIV viral reservoir.

Foundational 2015 paper – Campos, Tazi et al

Long lasting control of viral rebound with a new drug ABX464 targeting Rev – mediated viral RNA biogenesis

Noëlie Campos[1†], Renier Myburgh[3†], Aude Garcel[1†], Audrey Vautrin[2†], Laure Lapasset[2], Erika Schläpfer Nadal[3], Florence Mahuteau-Betzer[4], Romain Najman[1], Pauline Fornarelli[1], Katjana Tantale[2], Eugénia Basyuk[2], Martial Séveno[7], Julian P Venables[2], Bernard Pau[5], Edouard Bertrand[2], Mark A Wainberg[6], Roberto F Speck[3], Didier Scherrer[1] and Jamal Tazi[2*]

Abstract

Background: Current therapies have succeeded in controlling AIDS pandemic. However, there is a continuing need for new drugs, in particular those acting through new and as yet unexplored mechanisms of action to achieve HIV infection cure. We took advantage of the unique feature of proviral genome to require both activation and inhibition of splicing of viral transcripts to develop molecules capable of achieving long lasting effect on viral replication in humanized mouse models through inhibition of Rev-mediated viral RNA biogenesis.

Results: Current HIV therapies reduce viral load during treatment but titers rebound after treatment is discontinued. We devised a new drug that has a long lasting effect after viral load reduction. We demonstrate here that ABX464 compromises HIV replication of clinical isolates of different subtypes without selecting for drug resistance in PBMCs or macrophages. ABX464 alone, also efficiently compromised viral proliferation in two humanized mouse models infected with HIV that require a combination of 3TC, Raltegravir and Tenofovir (HAART) to achieve viral inhibition in current protocols. Crucially, while viral load increased dramatically just one week after stopping HAART treatment, only slight rebound was observed following treatment cessation with ABX464 and the magnitude of the rebound was maintained below to that of HAART for two months after stopping the treatment. Using a system to visualize single HIV RNA molecules in living cells, we show that ABX464 inhibits viral replication by preventing Rev-mediated export of unspliced HIV-1 transcripts to the cytoplasm and by interacting with the Cap Binding Complex (CBC). Deep sequencing of viral RNA from treated cells established that retained viral RNA is massively spliced but importantly, normal cellular splicing is unaffected by the drug. Consistently ABX464 is non-toxic in humans and therefore represents a promising complement to current HIV therapies.

Conclusions: ABX464 represents a novel class of anti-HIV molecules with unique properties. ABX464 has a long lasting effect in humanized mice and neutralizes the expression of HIV-1 proviral genome of infected immune cells including reservoirs and it is therefore a promising drug toward a functional cure of HIV.

Keywords: AIDS, RNA biogenesis, Splicing, New antiviral drug, HIV cure, Cap Binding Complex, Rev protein

"Rev Inhibitor" claim - the core purported mechanism

"…we show that ABX464 inhibits viral replication by preventing Rev-mediated export of unspliced HIV-1 transcripts to the cytoplasm…ABX464 which we show targets Rev function and therefore is susceptible to alter the viral expression in the reservoirs...

Claiming that it's a "functional cure" for HIV

"Crucially, while viral load increased dramatically just one week after stopping HAART treatment, only slight rebound was observed following treatment cessation with ABX464 and the magnitude of the rebound was maintained below to that of HAART for two months after stopping the treatment."

"ABX464 has a long lasting effect in humanized mice and neutralizes the expression of HIV-1 proviral genome of infected immune cells including reservoirs and it is therefore a promising drug toward a functional cure of HIV."

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC4422473/pdf/12977_2015_Article_159.pdf

The foundational paper for ABVX's HIV story was by Campos, Tazi et al -- remember these names, as they are central, suspect scientific actors to whom we return. Independent virologists audited the actual clinical tissue samples and debunked the claims -- the "Rev inhibitor" narrative collapsed.

Audited tissue samples debunked ABVX claims (Moron-Lopez et al, 2021); EACS 2017

ABX464 Decreases the Total Human Immunodeficiency Virus (HIV) Reservoir and HIV Transcription Initiation in CD4$^+$ T Cells From Antiretroviral Therapy–Suppressed Individuals Living With HIV

Sara Moron-Lopez,[1,2,a] Silvia Bernal,[3,4,a] Joseph K. Wong,[1,2] Javier Martinez-Picado,[3,4,5,b] and Steven A. Yukl[1,2,b]

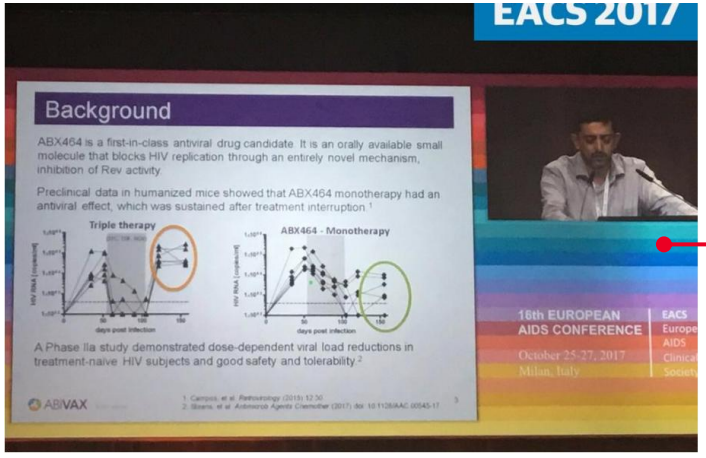
[1]Department of Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA; [2]Department of Medicine, University of California–San Francisco, San Francisco, California, USA; [3]IrsiCaixa AIDS Research Institute, Badalona, Spain; [4]University of Vic-Central University of Catalonia, Vic, Spain; and [5]Catalan Institution for Research and Advanced Studies, Barcelona, Spain

"We observed a significant decrease in total HIV DNA... and a lower median level of intact HIV DNA (P = not significant)...To further characterize its specific mechanism of action, long-term administration of ABX464 should be studied in a larger cohort."

"However, we observed no statistically significant change in multiply-spliced HIV transcripts, in contrast to a previous study…"

Thus, while total HIV DNA dropped, the drop in intact. replication-competent, proviral DNA was statistically insignificant -- the drug was clearing out harmless, dead viral fragments while leaving the actual virus pool intact.

ABX464 reduces HIV reservoir but doesn't delay viral rebound



EACS 2017: "Despite these reductions in HIV DNA there was no delay in HIV viral rebound in the ABX464 arm after treatment interruption compared to the placebo group, indicating that the degree of HIV DNA reduction was insufficient to affect the speed at which viral replication re-emerged after the interruption of treatment."

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC9187309/pdf/ciab733.pdf; https://www.aidsmap.com/news/oct-2017/abx464-reduces-hiv-reservoir-doesnt-delay-viral-rebound, citing Vandekerckhove L et al. *ABX464 decreases total HIV DNA in PBMCs when administered during 28 days to HIV-infected patients who are virologically suppressed.* 16th European AIDS Conference, 25-27 October, Milan, abstract PS 1/7, 2017.

ABVX reinvents the molecule's MOA every few years – in each reincarnation, miR-124 is "highly selective" for something new after the previous target failed. From 2015 to 2017, it was an "antiviral Rev inhibitor for HIV." They flipped the script in 2018, after that was debunked – it no longer selectively binds to CBC to inhibit viral Rev protein – it's now a "dual action" HIV antiviral plus bowel anti-inflammatory. The 2018 presentation shows a sprawling, contrived schematic in search of a coherent MOA story.

ABX464 – three different origin stories; purported mechanism is a moving target

2015-2017: HIV cure pitch – "First-in-class anti-HIV/Rev inhibitor"

ABX464



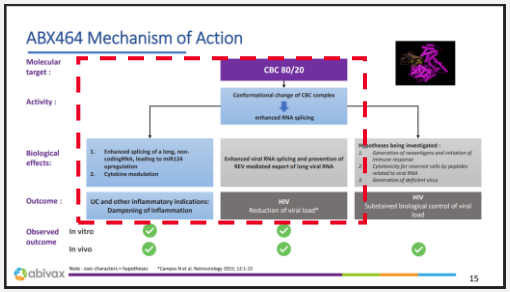
"ABX464 could become the central element of a functional cure for AIDS."

Professor Mark Wainberg, M.D., former President of the International AIDS Society and one of the top HIV experts worldwide

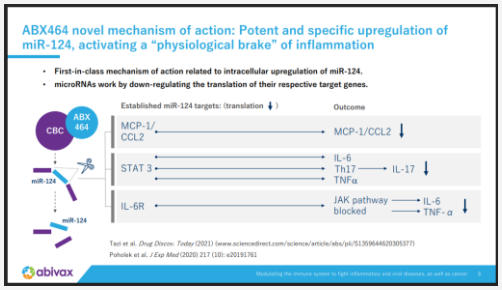
2018-2020: "Dual antiviral + anti-inflammatory RNA splicing"

Vautrin, Tazi et al (2019)

Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing



2021-present: a "clean" IBD rebrand as the "first-and-only oral miR-124 enhancer"



Source: https://www.abivax.com/wp-content/uploads/2018/10/ABIVAX_Corporate_Presentation-08Oct2018.pdf; https://www.nature.com/articles/s41598-018-37813-y;

In May 2020, Abivax re-branded again as a COVID play – "New data show ABX464 inhibits SARS-COV-2 viral replication...triple action, antiviral, anti-inflammatory, and tissue repair" – since dual-action was no longer contrived enough. Predictably, the trial flopped and was prematurely halted less than a year later. With ABVX then flip-flopping back to pushing a targeted, single-action story – now for UC -- its history of disingenuous scientific claims, stock promotion, and shifting MOA is self-evident

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Multiple May 14, 2020 press releases – COVID trial flopped, prematurely halted 10 months later

ABX464 INHIBITS REPLICATION OF SARS-CoV-2 (COVID-19) IN RECONSTITUTED HUMAN RESPIRATORY EPITHELIUM MODEL

ABX464 IS THE ONLY DRUG CANDIDATE WITH A POTENTIAL TRIPLE ACTION FOR COVID-19 TREATMENT: ANTIVIRAL, ANTI-INFLAMMATORY AND TISSUE REPAIR

******

ABIVAX RECEIVES ANSM AND ETHICS COMMITTEE CLEARANCE TO TEST ITS DEVELOPMENT CANDIDATE ABX464 IN 1,034 COVID-19 PATIENTS IN RANDOMIZED PHASE 2B/3 CLINICAL TRIAL

The breakthrough scientific data Abivax is reporting today make ABX464 a unique potential treatment for COVID-19 patients. Given the current pandemic and patient's excessive inflammatory response to viral replication as the primary cause of acute respiratory distress syndrome (ARDS) and death of COVID-19 patients, ABX464 with its convenient oral administration and its potential unique triple mode of action, will be urgently tested in a European clinical trial….

Trial shut down less than a year later as a failure, per Mar 5, 2021 press release

Sourcehttps://abivax.gcs-web.com/news-releases/news-release-details/abivax-follows-dsmb-recommendation-stop-phase-2b3-mir-age-covid; https://abivax.gcs-web.com/news-releases/news-release-details/abx464-inhibits-replication-sars-cov-2-covid-19-reconstituted; https://abivax.gcs-web.com/news-releases/news-release-details/abivax-follows-dsmb-recommendation-stop-phase-2b3-mir-age-covid

Abivax was founded by Philippe Pouletty of Truffle Capital – a controversial, serial French life sciences promoter who pumped ABX464 as a potential COVID cure. He co-founded the predecessor entity with Prof. Jamal Tazi in 2008, then merged three French biotech companies in 2013 to form Abivax.

Pouletty promoting ABVX for COVID on French TV, 2020



ABVX press release, 2017: Pouletty co-founded the predecessor entity then Abivax

"In 2008, Truffle Capital's Managing Director, Dr. Philippe Pouletty, founded Splicos in collaboration with Prof. Jamal Tazi and the CNRS with an exclusive global licensing agreement on Prof. Tazi's patent application on small molecules modulating RNA biogenesis. Under the impetus of Truffle Capital, ABIVAX was founded in December 2013 by merging three French biotech companies (Wittycell, Splicos and Zophis)."

Truffle Capital profile and LinkedIn bio: "the founder of Abivax" and ex-President



Philippe Pouletty, M.D.

CEO & Co-Founder

Linkedin ↗

Philippe Pouletty, M.D., is a serial Biotech and MedTech entrepreneur, inventor, with more than 30 years of experience building and scaling-up life-science companies in Europe and the United States. He is the co-founder and CEO of Truffle Capital, one of Europe's leading venture capital firms and the founder of Abivax, an $11Bn Biotech company, #1 in Europe, #3 Worldwide!. Abivax was the top stock market performance in Europe across all sectors in 2025, with a 1700% increase.



Dr Philippe Pouletty (MD) · 2nd

DG, cofondateur Truffle Capital, fondateur, ancien président d'Abivax, fondateur de Carvolix, d'Affluent Medical, Artedrone, Caranx, cofondateur de Carmat, Symetis, Vexim. Ancien président France Biotech & VP Europabio

Source: https://www.youtube.com/watch?v=v_prlGonrT4; https://www.truffle.com/biomedtech/team-biomedtech/philippe-pouletty-m-d; https://www.linkedin.com/in/philippe-pouletty/; https://ir.abivax.com/news-releases/news-release-details/prof-jamal-tazi-inventor-abx464-abivaxs-lead-drug-candidate/?utm_source=chatgpt.com

Pouletty has a long history of dubious microcap drug or medtech stock promotions that make grandiose claims, followed by safety-related recalls, regulatory scrutiny, and stock collapse. He first achieved notoriety as founder/CEO of SangStat -- the FDA revoked drug approval after a US recall.

Pouletty was founder, CEO, and Chairman of SangStat Medical at various times. The company was put out of its misery by Genzyme in a $600MM acquisition in 2003. SangStat's lead asset at the time was an anti-inflammatory compound for UC and Crohn's – the same indications as the ABVX story.

SangStat Medical's transplant drug pulled from market – its lead asset was RDP-58 for UC and Crohn's, which eventually failed in Phase 2

RDP58 is a novel and potentially effective oral therapy for ulcerative colitis

SangStat Pulls Version of Transplant Drug

Nationwide Recall of SangCya Oral Solution

Sangstat's Plunge Has Some Singing 'Cheap' Stock's Praises

RDP-58 (SangStat Medical)

Martin M Holtmann [1]

Affiliations + expand

PMID: 14666431

Abstract

RDP-58, a decapeptide with inhibitory effects on tumor necrosis factor synthesis, is under development by SangStat Medical Corp for the potential treatment of Crohn's disease and ulcerative colitis; phase II trials for both these indications commenced in October 2001. SangStat also initiated a phase I trial in chemotherapy-induced diarrhea in the first quarter of 2003 and anticipates initiating phase I trials in the gastrointestinal complications of HIV by the end of 2003.

Source: SangStat SEC filing lists Pouletty as founder, CEO, Chairman https://www.sec.gov/Archives/edgar/data/913610/000091361000000011/0000913610-00-000011-d1.htmll; https://pubmed.ncbi.nlm.nih.gov/14666431/; https://www.latimes.com/archives/la-xpm-2000-jul-11-fi-51015-story.html; https://www.thestreet.com/investing/stocks/sangstats-plunge-has-some-singing-cheap-stocks-praises-1129447; https://jamanetwork.com/journals/jama/article-abstract/1843316;

More recently, he co-founded Carmat – an absurd artificial heart promotion whose trial was halted after multiple fatalities – with Pouletty again pumping the stock on French TV: "La prothese cardiaque fonctionne tres bien." It even tried online crowdfunding to avert its 2026 delisting as a €0.10 stock.

Carmat filed for insolvency in 2025. The first patient died after 74 days, and the pivotal trial was suspended in 2017 after the 5th fatality.

Carmat was forced into liquidation and delisted in Jan 2026, after heavy scrutiny by French media

Fourth Patient Treated with Carmat Artificial Heart Dies

Carmat suspends pivotal trial for artificial heart in face of expanded regulatory scrutiny

Artificial heart maker Carmat suspends implants due to quality issue

Carmat stumbles after the death of a hidden patient

Prosthesis Artificial heart, a fourth death, and unanswered questions

In the middle of the night, the Carmat company announced the death of the fourth patient with the implant. Still very little information. What if this heart was, in fact, too large?



"La prothèse cardiaque fonctionne très bien" – Philippe Pouletty, BFM Business interview

Source: https://www-ix7-migration.dailymotion.com/video/x3uvxg1; https://www.reuters.com/markets/commodities/artificial-heart-maker-carmat-suspends-implants-due-quality-issue-2021-12-03/; https://www.reuters.com/markets/commodities/artificial-heart-maker-carmat-suspends-implants-due-quality-issue-2021-12-03/; https://www.liberation.fr/france/2016/01/21/coeur-artificiel-un-quatrieme-mort-et-des-questions-sans-reponse_1427925/; https://www.lalettre.fr/fr/entreprises/2016/01/21/carmat-trebuche-apres-le-deces-d-un-patient-cache,108126649-art

Pouletty finally won the lottery with ABVX -- a typical pump with a revolving door with two CEO's, and five Chief Medical Officers since 2021. Sheldon Sloan's abrupt, fake "retirement" as CMO is troubling, given his pre-eminent UC background and marquee Pfizer/Arena exit -- and puzzling replacement.

The CMO turnover is troubling as it overlaps with the duration of Phase 3 – typically a red flag that the trial is performing poorly. Sloan was their marquee CMO hire and barely lasted a year. His departure was buried at the bottom of a Jul 15, 2024 press release: "After 37 years of clinical medicine…Dr. Sloan has decided to retire." A few months later on Oct 1, Spyre Therapeutics (NASDAQ: SYRE, ~$9B market cap) announced Sloan as its new CMO. His replacement as CMO struck us as a downgrade vs. Sloan's bio.

Chief Medical Officer turnover – triumphant press release announcing Sloan's hiring as CMO in 2023; his "retirement" and replacement by Cataldi buried deep at the end of a 2024 "update"

2015-2021	Jean-Marc Steens
Mar 2021-Feb 2023	Sophie Biguenet
Feb 2023-Jul 2024	Sheldon Sloan
Jul 2024-Sep 2026	Fabio Cataldi
Sep 2026-present	Chris Rabbat

Feb 2023

ABIVAX APPOINTS DR. SHELDON SLOAN, M.D., AS CHIEF MEDICAL OFFICER

"We are excited to welcome Sheldon at Abivax and to benefit from his vast experience to drive the clinical and medical strategy and development of our Company in the years to come…"

Jul 2024

ABIVAX PROVIDES OPERATIONAL AND KEY PROGRAM UPDATE

"…we are pleased to announce the appointment of Dr. Fabio Cataldi as Chief Medical Officer…the Company also announces Dr. Sheldon Sloan, MD, M Bioethics will be leaving his role as Chief Medical Officer. After 37 years of clinical medicine and various roles in the Pharmaceutical Industry, Dr. Sloan has decided to retire."

Source: https://ir.abivax.com/news-releases/news-release-details/abivax-appoints-dr-sophie-biguenet-chief-medical-officer/; https://ir.abivax.com/news-releases/news-release-details/abivax-appoints-dr-sheldon-sloan-md-chief-medical-officer; https://ir.abivax.com/news-releases/news-release-details/abivax-provides-operational-and-key-program-update; https://ir.abivax.com/news-releases/news-release-details/abivax-presents-business-updates-and-first-half-2026-financial/; ABVX site lists Rabbat as current CMO

Chapter 3. The scientific rot at ABVX runs deep

Pouletty's co-founder is Prof. Jamal Tazi, "the inventor of ABX464" listed on the two key patents – whose foundational Abivax publications remind us of the proverb "to hide a lie, a thousand lies are needed." Every key ABVX miR-124 paper traces back to Tazi. We note his group's prior phony claims of the drug being an "unprecedented advance" for HIV.

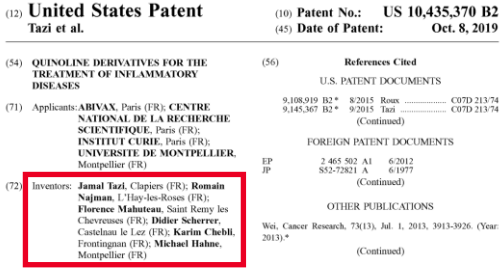
Tazi is a professor at the University of Montpelier and has held a variety of previous roles at Abivax: Vice President of Research, member of its Executive Committee and Scientific Advisory Board, and Head of the Collaborative Abivax-CNRS Laboratory.

Abivax co-founder and "inventor" of ABX464 Jamal Tazi – pattern of promotional claims about the drug's antiviral properties for HIV

Moroccan Researcher Develops Molecule that Slows AIDS Replication



PROF. JAMAL TAZI, INVENTOR OF ABX464, ABIVAX'S LEAD DRUG CANDIDATE FOR INDUCING A FUNCTIONAL CURE FOR HIV, AWARDED THE CNRS MEDAL OF INNOVATION 2017



(12) **United States Patent**
Tazi et al.

(10) **Patent No.: US 10,435,370 B2**
(45) **Date of Patent: Oct. 8, 2019**

(54) **QUINOLINE DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISEASES**

(71) Applicants: **ABIVAX**, Paris (FR); **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE**, Paris (FR); **INSTITUT CURIE**, Paris (FR); **UNIVERSITE DE MONTPELLIER**, Montpellier (FR)

(72) Inventors: **Jamal Tazi**, Clapiers (FR); **Romain Najman**, L'Hay-les-Roses (FR); **Florence Mahuteau**, Saint Remy les Chevreuses (FR); **Didier Scherrer**, Castelnau le Lez (FR); **Karim Chebli**, Frontignan (FR); **Michael Hahne**, Montpellier (FR)

(56) **References Cited**

U.S. PATENT DOCUMENTS

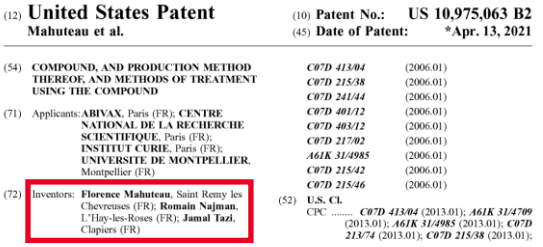
9,108,919 B2 * 8/2015 Roux C07D 213/74
9,145,367 B2 * 9/2015 Tazi C07D 213/74
(Continued)

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JP S52-72821 A 6/1977
(Continued)

OTHER PUBLICATIONS

Wei, Cancer Research, 73(13), Jul. 1, 2013, 3913-3926. (Year: 2013).*
(Continued)



(12) **United States Patent**
Mahuteau et al.

(10) **Patent No.: US 10,975,063 B2**
(45) **Date of Patent: *Apr. 13, 2021**

(54) **COMPOUND, AND PRODUCTION METHOD THEREOF, AND METHODS OF TREATMENT USING THE COMPOUND**

(71) Applicants: **ABIVAX**, Paris (FR); **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE**, Paris (FR); **INSTITUT CURIE**, Paris (FR); **UNIVERSITE DE MONTPELLIER**, Montpellier (FR)

(72) Inventors: **Florence Mahuteau**, Saint Remy les Chevreuses (FR); **Romain Najman**, L'Hay-les-Roses (FR); **Jamal Tazi**, Clapiers (FR)

C07D 413/04 (2006.01)
C07D 215/38 (2006.01)
C07D 241/44 (2006.01)
C07D 401/12 (2006.01)
C07D 403/12 (2006.01)
C07D 217/02 (2006.01)
A61K 31/4985 (2006.01)
C07D 215/42 (2006.01)
C07D 215/46 (2006.01)

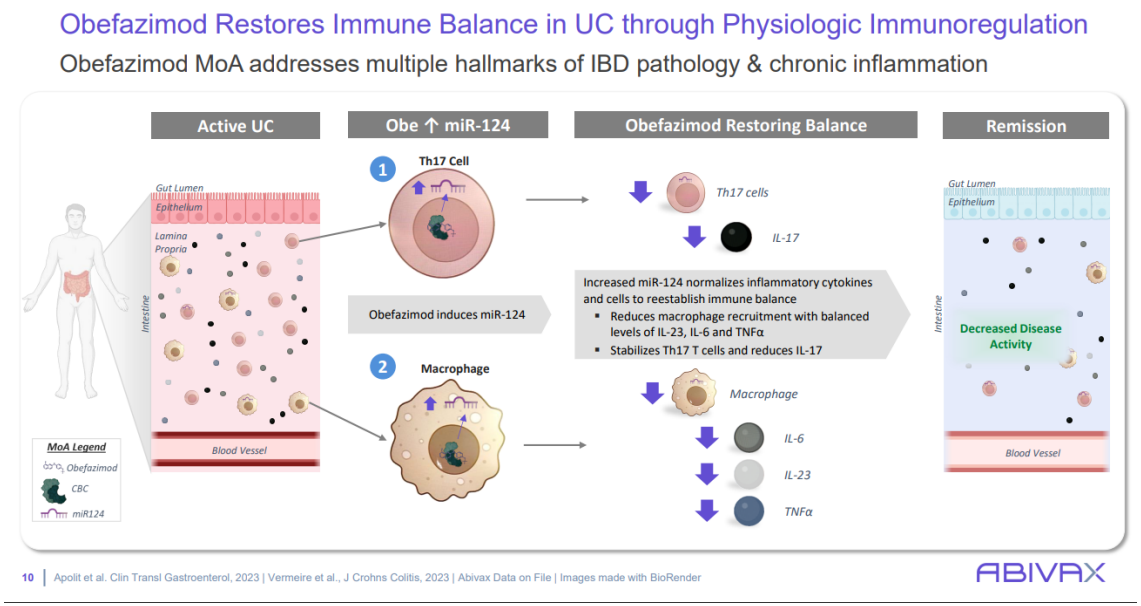
(52) **U.S. Cl.**
CPC ***C07D 413/04*** (2013.01); ***A61K 31/4709*** (2013.01); ***A61K 31/4985*** (2013.01); ***C07D 213/74*** (2013.01); ***C07D 215/38*** (2013.01);

"A research group…headed by Tazi have announced a breakthrough discovery that will potentially revolutionize AIDS research and treatment. The team developed a new molecule, ABX464, which attacks AIDS….The development is an "unprecedented advance in the scientific world," said the research group in a communiqué...ABX464 attacks the reservoir so that the virus does not replicate…" states Tazi" – Morocco World News, 2017

Source: https://www.moroccoworldnews.com/2017/05/99587/moroccan-researcher-develops-molecule-slows-aids-replication/; https://ir.abivax.com/news-releases/news-release-details/prof-jamal-tazi-inventor-abx464-abivaxs-lead-drug-candidate; https://patentimages.storage.googleapis.com/28/36/82/3cb0d2b7b00b40/US10975063.pdf; https://patentimages.storage.googleapis.com/09/75/b4/3740697fba32c7/US10435370.pdf; https://ir.abivax.com/static-files/6d6f2680-2b0b-4103-927c-0a0a3a13df0e; https://fr.wikipedia.org/wiki/Jamal_Tazi

ABVX's purported MOA is a blatant, sloppy scientific scam – hiding in plain sight for anyone who bothers to read Tazi's foundational ABVX papers. Before we pull the curtain, we note that their entire anti-inflammatory story hinges on miR124-upregulation in macrophages – per ABVX's own slides.

The entire obefazimod UC anti-inflammatory narrative hinges on miR-124 being upregulated within macrophages (Abivax corporate presentation, July 2026)



- **ABVX's anti-inflammatory story starts with macrophages.** Their own slides say miR-124 must be upregulated in macrophages to reduce key inflammatory cytokines.
- **If macrophages are not meaningfully suppressed, the rest of the story falls apart.** Macrophages drive IL-23, IL-6, TNF-alpha and MCP-1, which then sustain downstream inflammation.
- **T-cell effects alone are not enough.** If macrophages keep producing IL-23 and other cytokines, downstream Th17 / IL-17 signaling remains active.
- **That makes macrophage miR-124 the critical choke point.** If obefazimod fails to upregulate miR-124 in macrophages, its proposed UC mechanism is fundamentally undermined.

Source: https://analyticsplus.org/glossary/;

In 2019, Tazi was senior author on a paper that found ABX464 results in *no* miR-124 expression in macrophages. In a 2023 paper - after ABVX's pivot to UC - he claimed 9-fold increase in macrophage, contradicting his published data without explanation for the reversal or reference to the 2019 finding.

The same senior author (Tazi) reported in 2019 that miR-124 expression was "undetectable" in macrophages treated with ABX464, then reported in 2023 that it produced "9-fold" upregulation of miR-124 in macrophages. The 2023 paper makes no reference to the 2019 finding and offers no explanation for the reversal. The 2023 Discussion then builds ABVX's current mechanistic UC narrative on a result that contradicts the group's prior published data: "ABX464, by upregulating miR-124 in macrophages, will also limit their activation and secretion of proinflammatory cytokines including IL23 and IL6."

Jamal Tazi – blatant contradiction in two foundational ABVX papers, 2019 and 2023

Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing

Audrey Vautrin[2], Laurent Manchon[1], Aude Garcel[2], Noëlie Campos[2], Laure Lapasset[2], Abdelhamid Mahdi Laaref[1], Roman Bruno[3], Marie Gislard[4], Emeric Dubois[4], Didier Scherrer[2], J Hartmut Ehrlich[2] & Jamal Tazi[1]

specific cell types. Using purified CD4+, CD8 and macrophages cells, we found that ABX464 treatment resulted in upregulation of miR-124 in lymphoid cells (Fig. 3C) but not in monocyte-derived macrophages, where the expression of miR-124 was undetectable (Figs 3C and S4B). Finally, we proved that this upregulation of miR-124

*"ABX464 treatment resulted in upregulation of miR-124 in lymphoid cells (Fig. 3C) **but not in monocyte-derived macrophages, where the expression of miR-124 was undetectable** (Figs 3C and S4B)"*

ABX464 (Obefazimod) Upregulates miR-124 to Reduce Proinflammatory Markers in Inflammatory Bowel Diseases

Cécile Apolit, PhD[1,*], Noëlie Campos, PhD[1,*], Audrey Vautrin, PhD[1], Christina Begon-Pescia, PhD[2], Laure Lapasset, PhD[1], Didier Scherrer, PhD[1], Paul Gineste, PharmD[3], Hartmut Ehrlich, MD[3], Aude Garcel, PharmD, PhD[1], Julien Santo, PhD[1] and Jamal Tazi, PhD[1,3]

purified CD4+ cells, and macrophages. In this analysis, ABX464 treatment resulted in significant upregulation of miR-124 levels; specifically, the increases in miR-124 levels were 9-fold in PBMCs (Figure 1a), 7-fold in purified CD4+ cells (Figure 1b), and 9-fold in macrophages (Figure 1c). Cytokine analysis revealed that after

*"ABX464 treatment resulted in significant upregulation of miR-124 levels; specifically, the increases in miR-124 levels were 9-fold in PBMCs (Figure 1a), 7-fold in purified CD41 cells (Figure 1b), **and 9-fold in macrophages** (Figure 1c)"*

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC6349857/pdf/41598_2018_Article_37813.pdf; https://www.ovid.com/10.14309/ctg.0000000000000560

Tazi's conflicting, inept papers illustrate a common pattern in biotech frauds – the rig is hiding in open view, if one just bothers to read the key papers. True to form, his career-defining RNA-binding paper was subject to a rare, severe retraction by a key journal – his "ghost" co-authors simply vanished.

A highly-cited landmark paper from Tazi's laboratory was retracted after independent researchers discovered serious issues, which contaminated later published research. Tazi was the senior and corresponding author, not a peripheral collaborator. The details are ugly -- the independent researchers reported receiving flawed constructs from Tazi's lab twice, many years apart. The false mechanistic claim circulated for approximately two decades, polluting downstream literature.

Formal "Retract and Replace" Notice by the Journal of Cell Biology, 2023 – journals rarely resort to this mechanism, reserving it for highly-cited papers with a massive, corrupting flaw

Formal retraction notice suggests some of his co-authors disappeared: "We were unable to contact authors…"

JCB Journal of Cell Biology

RETRACT AND REPLACE

Retract and Replace: The RasGAP-associated endoribonuclease G3BP assembles stress granules

Hélène Tourrière, Karim Chebli, Latifa Zekri, Brice Courselaud, Jean Marie Blanchard, Edouard Bertrand, and Jamal Tazi

Vol. 160, No. 6 | https://doi.org/10.1083/jcb.200212128 | March 17, 2003

The *Journal of Cell Biology* retracts Tourrière et al. (2003. https://doi.org/10.1083/jcb.200212128) further to findings described in Panas et al. (2019) and Tourrière and Tazi (2019) showing that the G3BP1 phosphomimetic mutant construct (pEGFP-C1-G3BP1-S149E) also contains an aberrant S99P mutation, invalidating a subset of the findings in Figs. 4 B and 5 B that relied upon this construct.

Since the remaining data that do not rely on this flawed construct continue to support the conclusion that G3BP1 regulates stress granule assembly and that Ras signaling modulates this process, the article has been replaced, removing the relevant sections of Figs. 4 B and 5 B and the conclusions drawn from those experiments (2023. https://doi.org/10.1083/jcb.200212128072023new).

Authors Hélène Tourrière, Karim Chebli, Latifa Zekri, Edouard Bertrand, and Jamal Tazi agree with the retraction of Tourrière et al. (2003) and replacement with Tourrière et al. (2023) as described above. We were unable to contact authors Brice Courselaud and Jean Marie Blanchard.

Tazi initially refused to back down, publishing a defensive reply to salvage the paper vs. apologizing or gracefully issuing a retraction

REPLY

Reply to "Phosphorylation of G3BP1-S149 does not influence stress granule assembly"

Hélène Tourrière and Jamal Tazi

In this issue, Panas et al. (2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201801214) challenge the data published in the Tourrière et al. (2003. *J. Cell Biol.* https://doi.org/10.1083/jcb.200212128) paper on the role of G3BP phosphorylation in stress granule (SG) assembly. This reply addresses that letter and suggests that more work is needed to understand the role of this modification in SG formation.

In this issue, Panas et al. publish a refutation article putting into question the impact of G3BP phosphorylation on its S149 residue in G3BP-mediated assembly of stress granules (SGs) that we originally reported in Tourrière et al. (2003). They identified additional mutations that were accidently introduced in two plasmids expressing pEGFP-G3BP1 phosphomutant isoforms, which we originally generated and shared with numerous groups, including the authors. Indeed, they identified an alanine to threonine replacement at position 54 in the pEGFP-C1-G3BP1-S149A mutant and a serine to proline substitution at position 99 in pEGFP-C1-G3BP1-S149E. Therefore, they constructed a new set of G3BP1 mutant isoforms with a specific single mutation (A54T, S99P, S149A, and S149E) to dissect the effects of each site on SG assembly. They found that a construct containing only

we showed that arsenite treatment diminished the phosphorylation of S149 of endogenous G3BP by 50%, using in vivo labeling and immunoprecipitation of phosphorylated G3BP. In their letter, Panas et al. (2019) have used mass spectrometry (MS) analysis to quantify the phosphorylation status of S149. Due to the high content of acidic residues surrounding S149 leading to poor recovery, it is difficult if not impossible to have a rigorous quantification of phosphorylated G3BP. Hence, in our opinion, MS analysis alone may not be sufficient to precisely measure the phosphorylation status of S149. If the authors would like to make this point, they should use stable isotope labeling using amino acids in cell culture (SILAC) in combination with MS analysis to quantitively determine the impact of stress on G3BP phosphorylation. Third, we showed that the acidic domain

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10482727/pdf/JCB_20021212808022023r.pdf; https://rupress.org/jcb/article/218/7/2433/120974/Reply-to-Phosphorylation-of-G3BP1-S149-does-not

The landmark, embarrassing Tazi retraction was driven by independent scientists who audited his research – sleuths on PubPeer have flagged severe data discrepancies across other Tazi papers, detailing classic red flags for image integrity such as duplication and recycling across papers.

In one paper, a PubPeer user pointed out a classic image integrity red flag in Figure 1 (panels G and H) -- “much more similar than expected" loading controls: The comment isolates the gel bands, which are used as a baseline loading control to prove equal amounts of sample were tested. A thread on a second paper (right) flags potential image duplication and gel rotation across multiple Tazi papers.

Pubpeer – image/data integrity red flags identified by users on various papers by Jamal Tazi

Topoisomerase I and II inhibitors control caspase-2 pre-messenger RNA splicing in human cells

Molecular Cancer Research (2004) - 1 Comment

pubmed: 14757846 issn: 1541-7786

Stéphanie Solier, Amélie Lansiaux, Emmanuelle Logette, Jane Wu, Johann Soret, Jamal Tazi, Christian Bailly, Lydie Desoche, Eric Solary, Laurent Corcos

#1 ***Corydalis incisa*** comment accepted June 2024

Figure 1. Much more similar than expected.

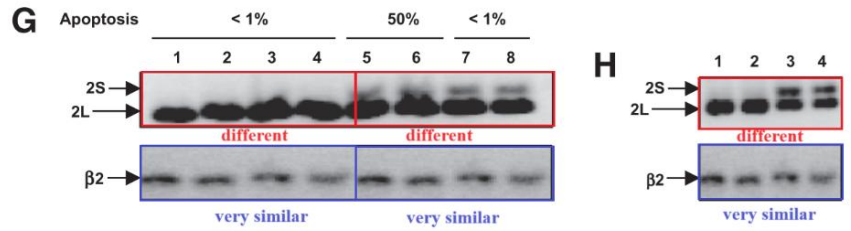


Figure 1 Mol Cancer Res . 2004 Jan;2(1):53-61.

Interaction between the small-nuclear-RNA cap hypermethylase and the spinal muscular atrophy protein, survival of motor neuron

The EMBO Reports (2003) - 3 Comments

doi: 10.1038/sj.embor.embor863 pubmed: 12776181 issn: 1469-221x issn: 1469-3178

John Mouaikel, Usha Narayanan, Céline Verheggen, A Gregory Matera, Edouard Bertrand, Jamal Tazi, Rémy Bordonné

#1 ***Mycosphaerella arachidis*** comment accepted January 2024

Figure 4A: The Anti-SMN and Anti-GFP bands appear to be rotations of each other. I've added the red shapes to show where I mean.

Could the authors please check and comment?



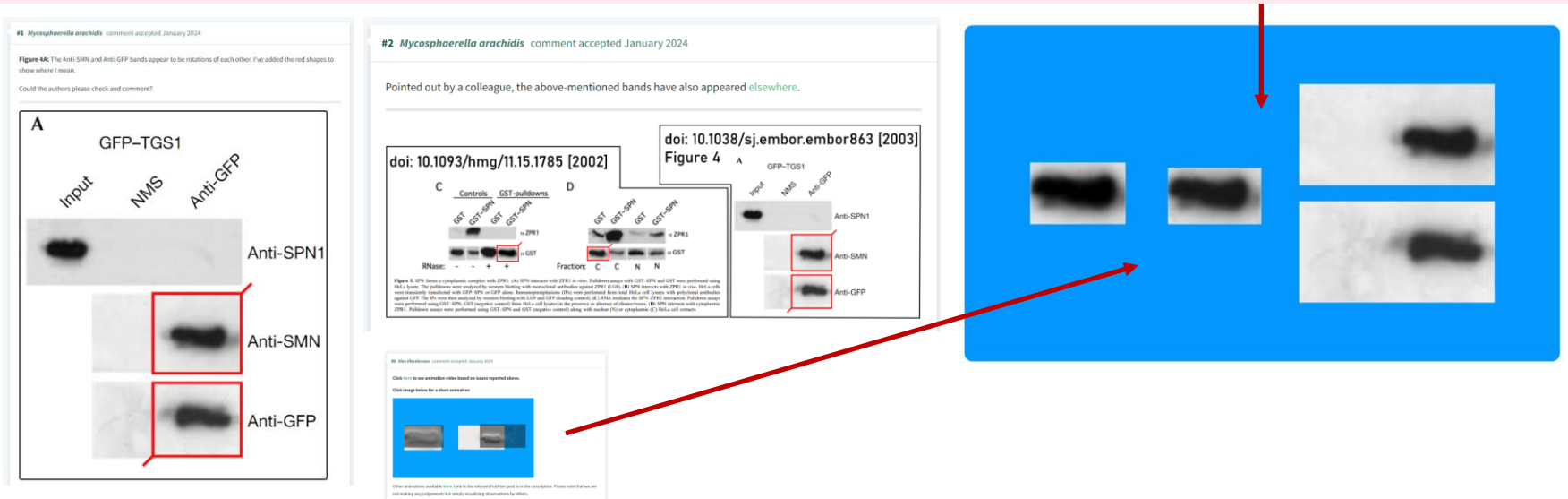
Source: https://pubpeer.com/publications/93C782ADC6A56872335D9A97C1D2A5; https://pubpeer.com/publications/D748048FE3C80BB563255B28760B2A

Discrepancies in Tazi papers flagged by multiple researchers are startling – reminding us of other high-profile scientific frauds. Investigators have even uploaded multiple animations to PubPeer + YouTube exposing the red flags.

A thread on a second paper flags potential image duplication and gel rotation. A user notes that the Western blot band labeled "Anti-SMN" and the band labeled "Anti-GFP" in Figure 4A appear to be rotations of each other, outlining both blocks in red shapes to show how the shapes, background smudges, and protein signal contours match almost perfectly when flipped or rotated, suggesting that a single gel image was repurposed to represent two entirely different antibody stains. Another comment expands the allegation, pointing out that the same bands appear to have been published across different papers over multiple years. Another user linked to an animation to overlay the flagged bands on top of one another to mathematically show that the background noise and band shapes are an identical match.

Pubpeer – image/data integrity red flags identified by users on papers by Jamal Tazi

YouTube link - animation to visually expose red flags: https://www.youtube.com/watch?v=voypcj7kPk8



Source: https://pubpeer.com/publications/93C782ADC6A56872335D9A97C1D2A5; https://www.youtube.com/watch?v=voypcj7kPk8

Birds of a feather flock together: the entire published ABX464 corpus emanates from a tiny, incestuous ring of ABVX researchers -- centered on Tazi as senior author on each key paper. Each foundational publication in the chain fails even the slightest scrutiny and exhibits retraction-worthy flags. The body of work is scant, only ~4 key papers – we scrutinize each.

Key papers – origin, mechanism, and miR-124 claim; each is ABVX-sponsored with Tazi as senior, corresponding author

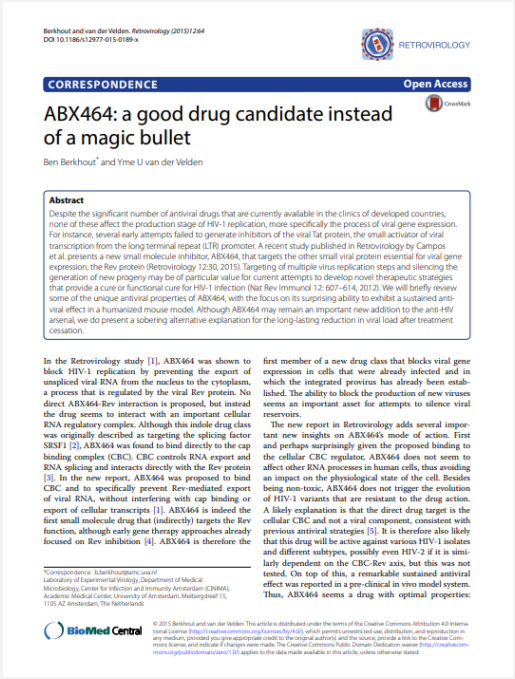
Long lasting control of viral rebound with a new drug ABX464 targeting Rev – mediated viral RNA biogenesis	**Campos, Tazi et al (2015) – first key paper and origin miR-124 document, everything else is downstream repurposing of this paper. Abivax paper with Tazi as senior author; Campos affiliation stated as Abivax.**
Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing	**Vautrin, Tazi et al (2019) – foundational mechanism paper for pivot from HIV to UC. Abivax paper with Tazi as senior author.Vautrin's LinkedIn bio states 14-year researcher tenure at ABVX.**
ABX464 (Obefazimod) Upregulates miR-124 to Reduce Proinflammatory Markers in Inflammatory Bowel Diseases	**Apolit, Tazi et al (2023) – principal paper used to connect drug exposure, mirR-124, and downstream inflammatory changes. Abivax paper with Tazi as senior author, Apolit affiliation stated as Abivax.**
The Anti-Hiv Candidate Abx464 Dampens Intestinal Inflammation by Triggering Il-22 Production in Activated Macrophages	**Chebli, Tazi et al (2017) – the original preclinical IBD/anti-inflammatory paper. Abivax paper with Tazi as senior author.**

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC4422473/pdf/12977_2015_Article_159.pdf; file:///C:/Users/kirka/Downloads/s41598-018-37813-y.pdf; https://pubmed.ncbi.nlm.nih.gov/36573890/; https://pubmed.ncbi.nlm.nih.gov/28687795/; https://pubmed.ncbi.nlm.nih.gov/28687795/

The field has smelled a skunk ever since Abivax's 2015 original CBC paper by Campos, Tazi et al. A rare, public peer-review challenge eviscerated and mocked its "magical…drug action" – undermining it as sloppy experimental flaw and artifact, and used the paper's own facts to show its purported explanation was biologically impossible and lacked basic scientific rigor.

A challenge this sharp is rare and significant in peer-reviewed science, typically occurring in less than 1% to 2% of studies. Standard academic critiques are usually wrapped in polite jargon -- rarely this brutal.

Peer-review challenge to original ABVX paper: "...one should entertain and exclude indirect effects when a magical sustained drug action is observed…"



Berkhout and van der Velden. *Retrovirology (2015)12:64*
DOI 10.1186/s12977-015-0189-x

RETROVIROLOGY

CORRESPONDENCE Open Access

ABX464: a good drug candidate instead of a magic bullet

Ben Berkhout* and Yme U van der Velden

Abstract

Despite the significant number of antiviral drugs that are currently available in the clinics of developed countries, none of these affect the production stage of HIV-1 replication, more specifically the process of viral gene expression. For instance, several early attempts failed to generate inhibitors of the viral Tat protein, the small activator of viral transcription from the long terminal repeat (LTR) promoter. A recent study published in Retrovirology by Campos et al. presents a new small molecule inhibitor, ABX464, that targets the other small viral protein essential for viral gene expression, the Rev protein (Retrovirology 12:30, 2015). Targeting of multiple virus replication steps and silencing the generation of new progeny may be of particular value for current attempts to develop novel therapeutic strategies that provide a cure or functional cure for HIV-1 infection (Nat Rev Immunol 12: 607–614, 2012). We will briefly review some of the unique antiviral properties of ABX464, with the focus on its surprising ability to exhibit a sustained anti-viral effect in a humanized mouse model. Although ABX464 may remain an important new addition to the anti-HIV arsenal, we do present a sobering alternative explanation for the long-lasting reduction in viral load after treatment cessation.

In the Retrovirology study [1], ABX464 was shown to block HIV-1 replication by preventing the export of unspliced viral RNA from the nucleus to the cytoplasm, a process that is regulated by the viral Rev protein. No direct ABX464-Rev interaction is proposed, but instead the drug seems to interact with an important cellular RNA regulatory complex. Although this indole drug class was originally described as targeting the splicing factor SRSF1 [2], ABX464 was found to bind directly to the cap binding complex (CBC). CBC controls RNA export and RNA splicing and interacts directly with the Rev protein [3]. In the new report, ABX464 was proposed to bind CBC and to specifically prevent Rev-mediated export of viral RNA, without interfering with cap binding or export of cellular transcripts [1]. ABX464 is indeed the first small molecule drug that (indirectly) targets the Rev function, although early gene therapy approaches already focused on Rev inhibition [4]. ABX464 is therefore the first member of a new drug class that blocks viral gene expression in cells that were already infected and in which the integrated provirus has already been established. The ability to block the production of new viruses seems an important asset for attempts to silence viral reservoirs.

The new report in Retrovirology adds several important new insights on ABX464's mode of action. First and perhaps surprisingly given the proposed binding to the cellular CBC regulator, ABX464 does not seem to affect other RNA processes in human cells, thus avoiding an impact on the physiological state of the cell. Besides being non-toxic, ABX464 does not trigger the evolution of HIV-1 variants that are resistant to the drug action. A likely explanation is that the direct drug target is the cellular CBC and not a viral component, consistent with previous antiviral strategies [5]. It is therefore also likely that this drug will be active against various HIV-1 isolates and different subtypes, possibly even HIV-2 if it is similarly dependent on the CBC-Rev axis, but this was not tested. On top of this, a remarkable sustained antiviral effect was reported in a pre-clinical in vivo model system. Thus, ABX464 seems a drug with optimal properties:

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BioMed Central

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Undermined the findings as "artifact"

"...some caution is warranted because the sustained drug action may be an artifact of the pre-clinical model system" - reduced the original study's key, "perplexing" finding - weeks of viral suppression post-treatment - to experimental flaw rather than a therapeutic breakthrough.

"Sobering" and alternative simple explanation

"... we do present a sobering alternative explanation for the long-lasting reduction in viral load after treatment cessation"; "the absence of sufficient target cells would provide a very simple explanation for the observed lack of viral rebound" - implies the "sustained effect" was caused by cellular exhaustion, not drug efficacy, suggesting the virus didn't rebound because it had already killed off all the CD4+ T cells it could infect.

Abivax explanation is biologically impossible

"...ABX464 could never have blocked all reservoir formation as the drug was added only at day 52 after the experimental infection of the mice. In fact, all reservoirs will likely have been established already by that time" - the original paper argued that ABX464 prevented viral rebound by blocking a macrophage reservoir. A basic timeline critique showed that explanation is biologically impossible.

Questioned the experimental rigor

"...the authors could for instance have refuted this alternative scenario by including an untreated YU2-infected group to monitor the CD4+ T cell dynamics throughout the experiment " - a fundamental omission in the experiment, pointing out that the researchers failed to include a basic control group that would have easily proven or disproven their major claim.

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC4515925/pdf/12977_2015_Article_189.pdf

Chapter 4. A scientific foundation built on retracted Chinese paper-mill “science”

The scientific rot at ABVX runs deep – a Chinese paper central to its UC narrative was recently retracted by the publishing journal's Chief Executive Editor after an investigation by its "Research Integrity" group. The retraction notice suggests fraud – and notes that the authors failed to reply.

The retraction notice stated that "Following publication, concerns were raised regarding the integrity of the images in the published figures. An investigation by our internal Research Integrity department…was unable to confirm the validity of the data presented and we cannot vouch for its reliability."

Original 2020 paper + 2024 retraction notice – "RETRACTED" watermark is on the online PDF



frontiers in Oncology

ORIGINAL RESEARCH
published: 17 December 2020
doi: 10.3389/fonc.2020.570128

RETRACTED: Mir-124 Attenuates STAT3-Mediated TH17 Differentiation in Colitis-Driven Colon Cancer

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Background: Inflammation often induces regeneration to repair the tissue damage. However, chronic inflammation can transform temporary hyperplasia into a fertile ground for tumorigenesis. Here, we demonstrate that the miR-124 acts as a safeguard to inhibit the pro-inflammatory production and reparative regeneration.

Methods: The expression levels of miR-124 and IL-17, IFN-γ were detected by qRT-PCR. TH17 or TH1 cells were detected by flow cytometer, respectively. The binding of STAT3 to the promoter region of IL-17 gene was analyzed by Chip assay. miR-124 binding to the 3'UTR of STAT3 gene was detected by reported plasmid construction and luciferase assay. Furthermore, DSS-induced colitis mice model and T cell transfer model were used to confirm the function of miR-124 *in vivo*. The related gene expression was analyzed by ELISA and western blot experiments.

Results: The results indicated that miR-124 decrease promotes colon tumorigenesis after *Citrobacter rodentium* infection and AOM/DSS induced colon cancer murine model. The molecular mechanism, miR-124 targets STAT3 to inhibit TH17 cell polarization and reduce TH17 polarization in colonic microenvironment.

Conclusions: Our study strengthened the important role of miR-124 in the regulation of adaptive immune responses and blocking the development of colitis-related cancer.

Keywords: miR-124, STAT3, TH17 cell, colitis, colitis-related cancer

BACKGROUND

The development of colorectal cancer (CRC) is a process of host immune interaction between tumor and tumor microenvironment. Tumor cells secrete proinflammatory mediators, and immune cells secrete cytokines, which together can promote tumor process. Previous results have shown that the TH17 cells' percent are higher in human CRC tissues (1, 2), which could activate immune suppressive mediators' release, and weaken the activity of cytotoxic CD8⁺ cells to kill tumor cells

Abbreviations: CRC, Colitis-Related Cancer; miR-124, microRNA-124; qPCR, quantitative real-time PCR; DSS, Dextran Sulfate sodium salt; AOM, azoxymethane.

RETRACTED

Retraction: Mir-124 attenuates STAT3-mediated TH17 differentiation in colitis-driven colon cancer

Frontiers Editorial Office*

A Retraction of the Original Research Article

Mir-124 attenuates STAT3-mediated TH17 differentiation in colitis-driven colon cancer

by Lin S, Liu Q, Wen J, Bai K, Guo Y and Wang J (2020) *Front. Oncol.* 10:570128. doi: 10.3389/fonc.2020.570128

The journal retracts the 2020 article cited above.

Following publication, concerns were raised regarding the integrity of the images in the published figures. An investigation by our internal Research Integrity department, conducted in accordance with Frontiers policies, was unable to confirm the validity of the data presented and we cannot vouch for its reliability. The article is therefore retracted.

This retraction was approved by the Chief Executive Editor of Frontiers. The authors received a communication regarding the retraction and had a chance to respond. This communication has been recorded by the publisher.

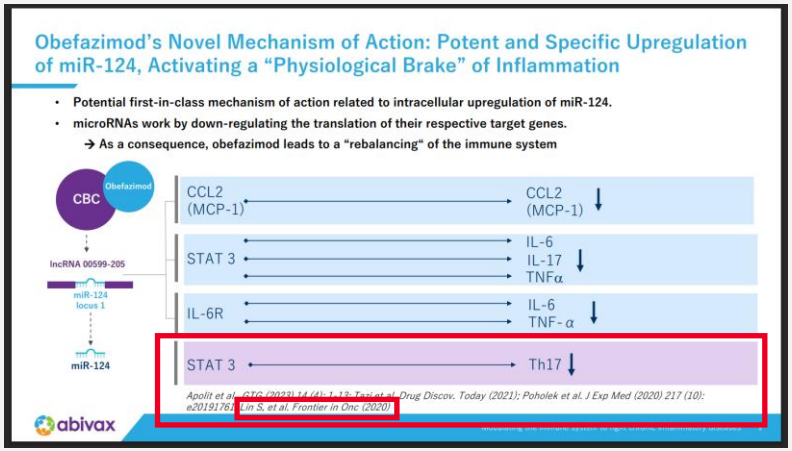
Source: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2020.570128/full; https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1506202/full

ABVX investor presentations have long cited the now-retracted Lin paper – featured on the main MoA slide as the key evidentiary support for the story that "selective mIr-124 upregulation halts inflammation": miR-124 → STAT3 suppression → Th17 dampening in UC. The citation is now opaque: "Abivax data on file"; the STAT3/Th17 reference is still sourced to a paper citing Lin.

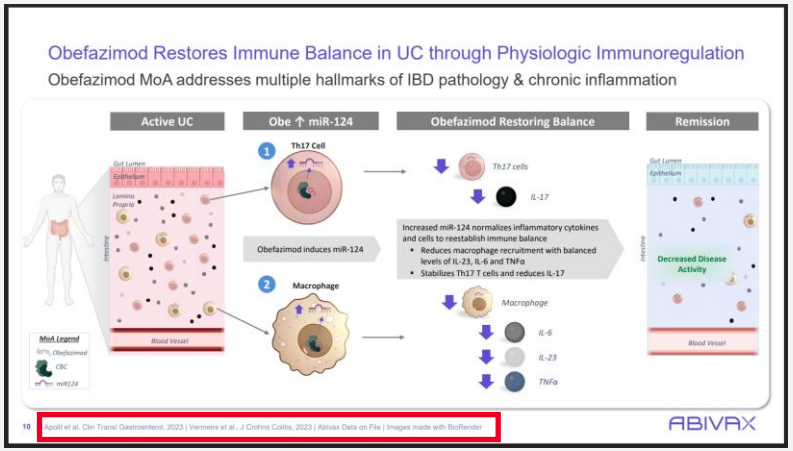
ABVX stopped naming Lin just before the retraction but continued presenting the Lin-dependent STAT3–Th17 mechanism, even though the study supplying the key evidence was retracted. ABVX has not cited an equivalent replacement study. Its current presentation attempts to reconstruct the former Lin mechanism from disconnected studies -- the citation ostensibly supporting the miR-124–STAT3 statement doesn't actually test STAT3 or Th17 activity. And another cited paper still cites and sources to Lin.

ABVX corporate presentations cite and/or rely upon the now-retracted Lin paper

Jun 2023 presentation, p9 – the only slide in the MoA section leans on Lin for the key graphic (STAT3/Th17); other 2022/2023 presentations used a similar slide



Current presentation (July 2026, p10) obscures the citation while still presenting the retracted Lin pathway



Source: https://www.abivax.com/wp-content/uploads/2023/06/Corporate_Presentation_Abivax_June2023.pdf; https://www.abivax.com/wp-content/uploads/2023/02/Abivax_Corporate_Presentation_Feb._2023.pdf; https://www.abivax.com/wp-content/uploads/2022/05/Corporate_Presentation_Abivax_May_2022.pdf

Remarkably, Vermeire 2025 – a foundational study with five ABVX co-authors -- continues to cite Lin long after its retraction. Abivax's July 2026 presentation now cites Vermeire on its key UC and Crohn's mechanism slides, creating a circular chain back to Lin, the study Vermeire relies on for the purported anti-inflammatory pathway's most direct support.

Obefazimod's entire clinical narrative rests on its ability to selectively upregulate miR-124 to reduce inflammation in UC and Crohn's. The retracted Lin study was foundational literature supporting that exact story – that miR-124 suppresses colitis and prevents it from progressing to colon cancer by inhibiting TH17 cells and the STAT3 pathway.

Vermeire 2025 cites Lin to claim miR-124 is "a natural regulator of the inflammatory response"; current ABVX July 2026 investor presentation cites Vermeire – a circular reference back to Lin

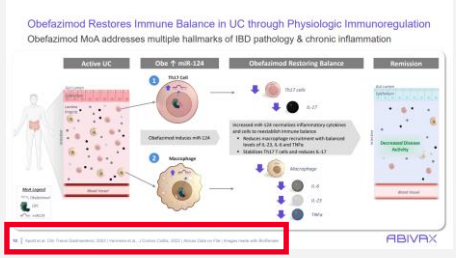
Vermeire et al 2025 cites Lin as the only complete colitis miR-124 → STAT3 → Th17 MoA citation in the footnote dump

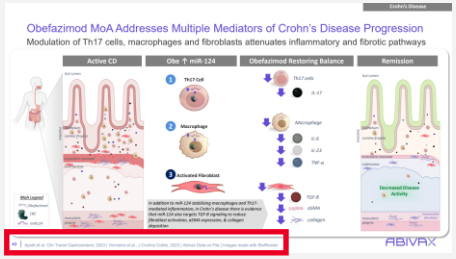
Obefazimod in patients with moderate-to-severely active ulcerative colitis: efficacy and safety analysis from the 96-week open-label maintenance phase 2b study

Obefazimod is an investigational, oral, once–daily (od), small molecule that enhances the expression of a single micro-RNA (miR)-124,[9–11] a natural regulator of the inflammatory response.[12–20] Evidence from human clinical trials and animal

13. Lin S, Liu Q, Wen J, Bai K, Guo Y, Wang J. Mir-124 Attenuates STAT3-Mediated TH17 differentiation in colitis-driven colon cancer. *Front Oncol.* 2020;**10**:570128.

ABVX July 2026 presentation – key UC and Crohn's MoA slides, circular reference





Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC12124117/pdf/jjaf074.pdf; https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d

The Lin retraction and ABVX papers epitomize the microRNA field – a scientific cesspool revolving around Chinese paper mills, with ~1,000 confirmed retractions and countless more evading scrutiny. The single-miR disease mechanism space -- miR-124 in particular – exhibits one of the most rampant research integrity and study fraud epidemics in science.

2025 and 2026 studies indicate a massive retractions epidemic in the microRNA study space

2025 study by a leading scientific forensic investigator

The entities enabling scientific fraud at scale are large, resilient, and growing rapidly

"…we investigated whether certain subfields are preferentially selected by those involved in scientific fraud…among those closely related subfields, paper mills are suspected to be particularly drawn to miRNAs, circular RNAs, and incRNAs."

2026 pre-print study

Analysis of the retraction papers in microRNA field from Chinese scholars between 2009 to 2022

"1063 retracted papers were identified…reasons for retraction were paper mills (48.3%), duplication of image (40.3%), and concerns/issues about data (37.2%)…retracted papers were from 42 publishers and 161 journals…top ten publishers accounting for 86.1% of retractions

Source: https://www.pnas.org/doi/10.1073/pnas.2420092122#sec-4; https://assets-eu.researchsquare.com/files/rs-8579411/v1/9770dfa4-6c8e-48cb-b318-5224cabfcc4a.pdf?c=1768560113

Specifically, the miR-124 validation literature that ABVX invokes and is directly exposed to is heavily polluted with fraudulent paper-mill studies, one of the most compromised corners of molecular biology -- miR-124 is one of the top 3 individual miRNA's most frequently appearing in the JAMA retraction corpus, along with miR-21 and 155, per a 2024 review.

The review analyzed articles on microRNAs retrieved from PubMed, Web of Science, and Retraction Watch. The core finding is sobering: "This systematic review of 887 retracted articles reporting microRNA biomarkers and 9574 control articles found that retraction was not associated with reductions in further citations and that compared with controls, publications citing retracted articles were more often retracted."

Review analyzed retracted microRNA articles and found that miR-124 was among the top 3

JAMA Network | Open

Original Investigation | Medical Journals and Publishing

Citations of microRNA Biomarker Articles That Were Retracted
A Systematic Review

from China. Most retracted articles (782 articles [88.16%]) focused on a single microRNA, with miR-21, miR-124, and miR-155 the 3 most frequently reported microRNAs. Cancer research contributed more than two-thirds of retracted miRNA articles (617 articles [69.56%]); 799 retracted articles reported diseases, and 162 articles reported long noncoding RNA (lncRNA).

Table. Characteristics of Retracted Studies

Characteristic	Studies, No. (%)
Country	
Single	842 (94.93)
China	756 (89.79)
US	39 (4.63)
Iran	20 (2.38)
Other	27 (3.21)
Multiple	36 (4.06)
Not reported	9 (1.01)
Citation after retraction, No. (No. citations)	
Not available[a]	64
0 citations	202 (0)
1 to <50 citations	603 (4365)
50 to <100 citations	12 (936)
≥100 Citations	6 (1026)
microRNA	
Single	782 (88.16)
miR-21	25 (2.82)
miR-124	19 (2.14)
miR-155	14 (1.58)
Other	724 (81.62)
Multiple	105 (11.84)

Sourcehttps://pmc.ncbi.nlm.nih.gov/articles/PMC10958238/

We found 63 retracted miR-124 papers, of which 8 are STAT3 papers, just like Lin's – ABVX's verbatim mechanistic chain and its anti-inflammatory story: miR-124 → STAT3 → Th17, in colitis. Given the uncanny, tidy mechanistic similarity, we assume that ABVX simply lifted its core narrative from the extensive Chinese paper mill corpus on miR-124/STAT3.

Eight miR-124/STAT3 retractions – obefazimod's core mechanistic claim

Row 8 (Lin, retracted) reproduces Abivax's end-to-end mechanism end to end — miR-124 → STAT3 → Th17 differentiation, in colitis.

	Retracted paper	Journal (publisher)	Published → Retracted	Stated reason for retraction
1	Up-regulation of miR-124 inhibits invasion and proliferation of prostate cancer cells through mediating JAK-STAT3 signaling pathway	Eur Rev Med Pharmacol Sci (Verduci)	May 2017 → Jul 2020	**PAPER MILL**; data and image concerns; original data not provided; author unresponsive
2	miR-124 inhibits proliferation and invasion of human retinoblastoma cells by targeting STAT3	Oncology Reports (Spandidos)	Aug 2016 → Sep 2021	**PAPER MILL**; image duplication
3	Knockdown of lncRNA XIST inhibits retinoblastoma progression by modulating the miR-124/STAT3 axis	Biomed. & Pharmacother. (Elsevier)	Aug 2018 → Mar 2022	**PAPER MILL**; image duplication
4	Long noncoding RNA SNHG14 promotes the aggressiveness of retinoblastoma by sponging microRNA-124 and thereby upregulating STAT3	Int. J. Molecular Medicine (Spandidos)	Mar 2020 → Mar 2022	**PAPER MILL**; image duplication; original data unavailable
5	High-intensity focused ultrasound inhibits invasion and metastasis of colon cancer cells by enhancing microRNA-124-mediated suppression of STAT3	FEBS Open Bio (Wiley)	May 2019 → Nov 2022	**PAPER MILL**; image duplication
6	Effects of miR-124-3p silencing on neuronal damage in the hippocampus of depression rats by regulating STAT3 gene	Comput. Math. Methods Med. (Hindawi)	Jun 2022 → Dec 2023	**PAPER MILL**; compromised peer review; unreliable results
7	MicroRNA-124-3p inhibits the growth and metastasis of nasopharyngeal carcinoma cells by targeting STAT3	Oncology Reports (Spandidos)	Dec 2015 → Sep 2024	Plagiarism of data; duplication of data; author unresponsive
8	**Mir-124 attenuates STAT3-mediated TH17 differentiation in colitis-driven colon cancer**	Frontiers in Oncology	Dec 2020 → Oct 2024	Image integrity concerns; unreliable data

Source: Retraction Watch Database (Center for Scientific Integrity), 71,476 records through 15 July 2026. Titles matched on (microRNA|miRNA|miR)-124 with digit exclusion; 63 miR-124 retractions identified, of which 8 concern STAT3. Retraction reasons quoted from the published notices.

Chapter 5. Obefazimod’s extreme physicochemical properties

ABX464's extreme physicochemical properties dictate its abnormal pharmacokinetic and toxicity profile – predictive of tissue loading, broad off-target effects, and aggregation. Most key properties lack disclosure, per our search[1], so we measured the metrics ourselves (in red, below).

Property	Scorpion, finding	Scorpion, method	Sponsor's disclosure[1]	Reported metric, source	Comments
log P	Measured 6.35	RP-HPLC by OECD Test Guideline 117	Not disclosed[1]	5.72, DrugBank 5.9, PubChem 6.2, ChemAxon	We reveal the only measured log P for ABX464, per our disclosure search
pKa	Measured neutral, pH 2 to 11	Intrinsic-fluorescence pH titration, pH 2 to 11	Not disclosed[1]	NA	CNS access, membrane loading, no lysosomal trapping
Melting point (MP)	NA	NA	120.5 °C	US 2024/0182422 A1	Used to calculate intrinsic solubility
Aqueous solubility	Intrinsic solubility, 0.16 µM (aggregate formation)	GSE calculated from measured log P and MP	Poor water solubility, patent and Campos	4.94 µM, DrugBank 5.01 µM, ALOGPS	Insoluble across many Abivax in vitro studies, most are single 5 µM readouts 31x above solubility
Aggregation, CAC	Complete aggregation ≤ 1 µM	Dynamic light scattering (DLS)	Forms aggregates, Campos 2015	NA	Confirmed intrinsic solubility 0.16 µM
Crystal transition	~5 µM shift Autofluorescence (430/480 nm)	Ratiometric fluorescence	Crystal form 1 melting point 120.5	NA	Aggregate to crystal transition in aqueous solution ~5 µM but solubility much lower at 0.16 µM
Fluorescence absorption spectrum	ε 8,400 $M^{-1}cm^{-1}$ (peak, 8.4-fold above ICH S10 threshold); 315 to 386 nm range over threshold	UV-Vis absorption spectrum in acetonitrile	N-Glu "...phototoxic in a nonclinical model at clinically relevant exposure levels"	NA	Molecule will excite deep in the skin layer where skin cancers originate. We estimate ABX464 will excite once every ~60 seconds in the dividing keratinocyte layer at 40 to 50 µm
Cytotoxicity	< 1 µM, linear increase DLS (Campos concentration audit) 0.16 µM, calculated	LC-MS/MS cell-free assay from Campos 2015; actual 5x lower than nominal	"not toxic to cells"	Campos states >60 µM; graph shows 28% cytotoxicity	Toxic to cells at all concentrations tested from 0.39 to 20 µM actual; 60 µM cytotoxicity threshold inflated 154-fold
AhR activation	AhR signature induction in mouse and man, 3.7-fold, 27.7-fold CYP1A1 ($p<0.01$)	Reanalysis of Abivax's transcriptome deposits	Activation by ABX464 not discussed. We found the signature in transcriptome libraries[1]	EC50 luciferase AhR 404 nM, Equillium	At 5 µM, AhR is 85% maximal and reversible by AhR antagonist
TPSA (topological polar surface area)	NA	NA	Not disclosed[1]	34.2 Å², PubChem	TPSA is used to calculate other metrics

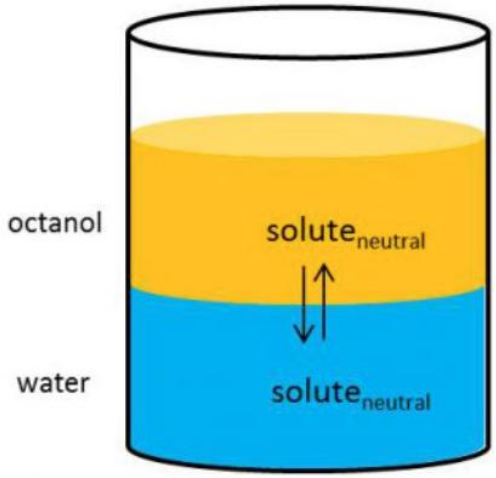
[1]Search terms we used. Lipophilicity: log P, logP, log D, lipophilic, lipophilicity, partition coefficient, octanol. Ionization: pKa, ionization state, ionisation, protonation state, net charge, acid dissociation. Solid state: melting point, melting range, DSC, XRPD, X-ray powder diffraction, polymorph, crystalline form, crystal form. Solubility and aggregation: aqueous solubility, water solubility, intrinsic solubility, critical aggregation concentration, CAC, dynamic light scattering, DLS, Z-average, nanoparticle, supersaturation. Spectroscopy: autofluorescence, intrinsic fluorescence, fluorophore, chromophore, molar extinction coefficient, absorption spectrum, UV-Vis. AhR: aryl hydrocarbon, AhR, xenobiotic, dioxin, CYP1A1, CYP1A2, CYP1B1, TIPARP, AHRR, NQO1. Surface area: TPSA, topological polar surface area. Case-insensitive, searched in English and French. Hits verified by reading the surrounding sentence.

Sources: Scorpion Capital research, literature/publication review, estimates, analysis, and lab experiments we commissioned

LogP is the standard metric to assess lipophilicity

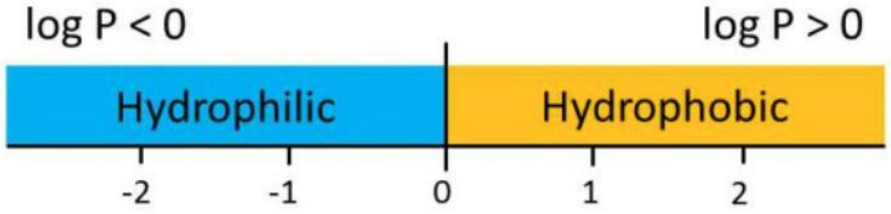
Lipophilicity means fat-loving. It measures a molecule's preference for dissolving in fats and oils versus water. Some dissolve easily in water (hydrophilic, like sugar or salt), some in fats and oils (lipophilic, like wax or grease). Most drugs fall in between. The standard measurement is logP - the logarithm of the partition coefficient. You take a test tube, put water in the bottom and octanol (a fatty alcohol that mimics biological lipids) on top, drop in the drug, let it separate, and measure the amount of drug in each layer.

LogP is the logarithm of the partition coefficient, representing a molecule's lipophilicity



Partition coefficient (log P) =

$$\frac{\textit{solute concentration dissolved in octanol}}{\textit{solute concentration dissolved in water}}$$

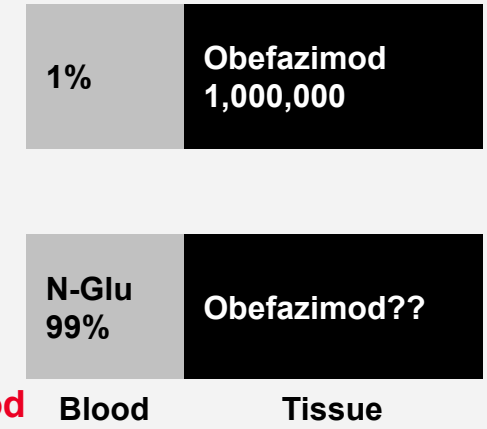


Source: https://analyticsplus.org/glossary/;

Obefazimod's computed logP of ~6 implies a million-to-one preference for lipid compartments over aqueous ones – experimentally-measured logP is even higher by almost 3X

Log P predicts the partitioning of compounds into lipid rich (octanal) vs cell membranes (water). A logP of 0 means the drug splits equally between fat and water. A logP of 1 means 10× more drug goes into fat than water. A logP of 2 means 100× more in fat. A logP of 3 means 1,000× more in fat. Obefazimod has a logP of approximately 6. For every 1 molecule that remains in the aqueous phase, roughly 1,000,000 partition into lipid — a million-to-one preference for fat over water. Obefazimod will concentrate in cell membranes at 10^6 times the level found in blood or GI fluid.

LogP	Octonal: Water Ratio = Lipid: Body Water Partition Coefficient
2	1:100
3	1:1,000
4	1:10,000
5	1:100,000
6	**1:1,000,000** ← **Obefazimod**
7	1:10,000,000



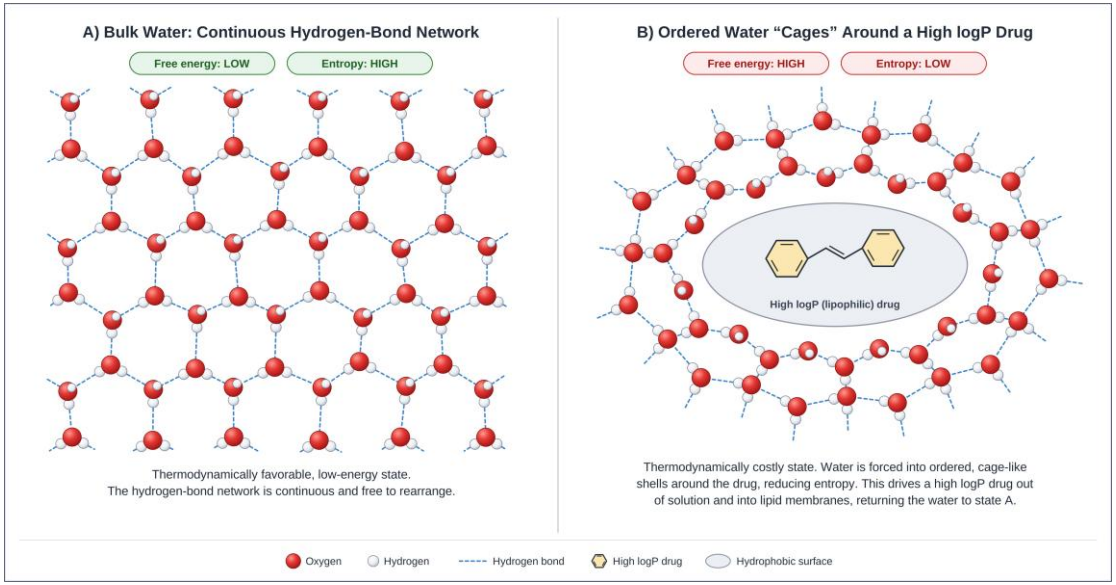
As a class

- Retained in cell membranes; and intracellular membranes – mitochondrial, ER, SR
- High levels in target tissues - gut, liver, pancreas
- In blood highly bound to HDL, LDL and albumin
- Rapidly leaves blood into tissues – <1 h half-life

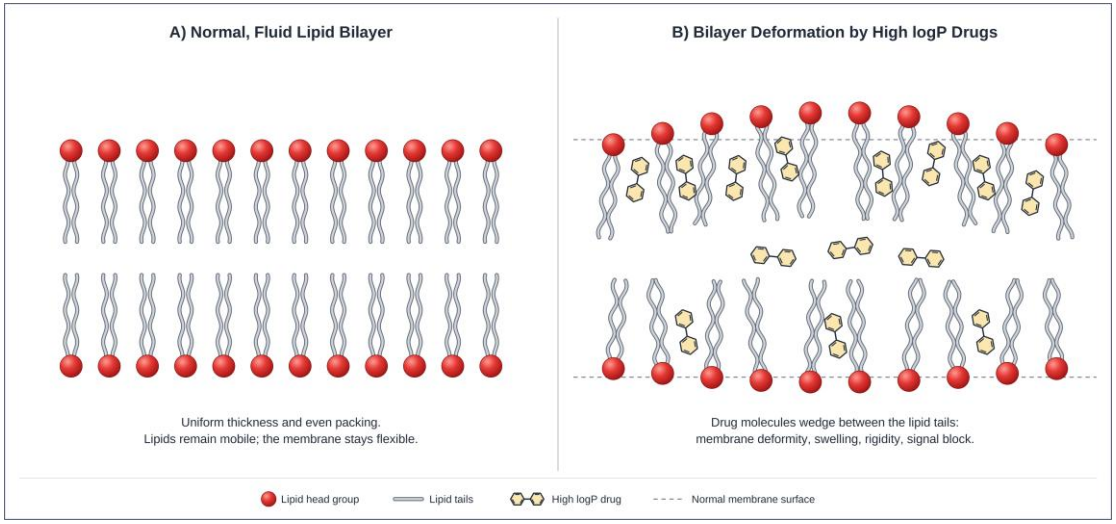
Obefazimod can be expected to accumulate in tissues. 99% of circulating obefazimod is N-glucuronidated metabolite

Source: Scorpion Capital research, estimates, and analysis

High-logP compounds like ABX464 are driven out of water and into lipid membranes, where accumulation can deform the bilayer. Illustrative visual.



Water excludes hydrophobic molecules, so a neutral high-logP compound like ABX464 is predicted to preferentially partition into lipid membranes



Rising membrane concentration disrupts the lipid bilayer, leading to swelling, rigidity, signal block, mitochondria dysfunction, and other nonspecific membrane effects

Sources: Fernández-Vidal et al. 2011; Jackson et al. 2016; Nagar et al. 2017; Scorpion Capital log P and pKa experiments; Scorpion Capital publication/literature review, estimates, and modeling.

A logP ~6 drug doesn't stay in bloodstream -- it buries into every lipid-rich compartment, from cell membranes to adipose tissue to the brain; accumulates with each dose; and doesn't fully clear.

A logP ~6 drug favors nonpolar, lipid-rich environments over aqueous ones and aggressively partitions into cell membranes, accumulate in lysosomes, and builds up in lipid-rich tissues with each dose. The body is a collection of water compartments separated by lipid membranes. Blood plasma, extracellular fluid, and the inside of cells are mostly water. Each cell is wrapped in a lipid bilayer membrane - a thin sheet of fat molecules. Organelles inside cells (lysosomes, mitochondria, endoplasmic reticulum) have their own lipid membranes. The brain is 60% fat by dry weight. Adipose tissue is almost entirely lipid.

Key Lipid Depots In The Body Where a LogP 6 Drug Will Aggressively Partition

01. Adipose tissue is the primary depot	With high lipophilicity, a logP 6 compound will accumulate extensively in body fat, which can act as a slow-release reservoir - leading to long elimination half-lives and accumulation with repeated dosing.
02. Cell membranes are the next key site	The phospholipid bilayer of cells Is a sink for lipophilic molecules to embed deeply within the hydrophobic core of the bilayer rather than just the membrane surface, leading to phospholipidosis.
03. Brain and CNS tissue	The brain is roughly 60% fat by dry weight, so highly lipophilic compounds partition readily into neural tissue
04. Liver	Hepatocytes are membrane-rich and highly perfused with blood, leading lipophilic drugs to accumulate here.
05. Lung tissue	Lung tissue is surprisingly lipophilic and highly perfused, making it another accumulation site - this is well-documented for high logP drugs.
06. Myelin sheaths	The lipid-rich insulation around nerve fibers is another partitioning site, leading to peripheral nerve and CNS distribution.
07. Skin and sebaceous glands	The stratum corneum and sebum are lipid-rich, so logP 6 compounds can accumulate in dermal layers.

Abivax has never publicly disclosed an experimentally measured LogP, to our knowledge -- a telling omission for a compound this lipophilic. Numerous independent computational sources confirm LogP ~6.

PubChem XLogP3 computes a logP of 5.9 for obefazimod. XLogP3 is a widely-used, highly accurate computational method for predicting the octanol-water partition coefficient and is the standard method used by the NIH's National Center for Biotechnology Information, calibrated on over 8,000 organic compounds. We show PubChem and DrugBank (citing Chemaxon and ALOGPS methods indicating logP of 5.7-6.2) below, results which are consistent with other widely-accepted models such as SwissADME. No computational method we can find returns a value below the Lipinski threshold of 5.

Various sources indicate obefazimod logP of ~6

Source 1: DrugBank DB14828 Source: https://go.drugbank.com/drugs/DB14828

Predicted Properties

PROPERTY	VALUE	SOURCE
Water Solubility	0.00159 mg/mL	ALOGPS
logP	5.72	ALOGPS
logP	6.2	Chemaxon
logS	-5.3	ALOGPS

Source 2: PubChem CID 49846599 – XPLogP3 Source: https://pubchem.ncbi.nlm.nih.gov/compound/49846599

3 Chemical and Physical Properties

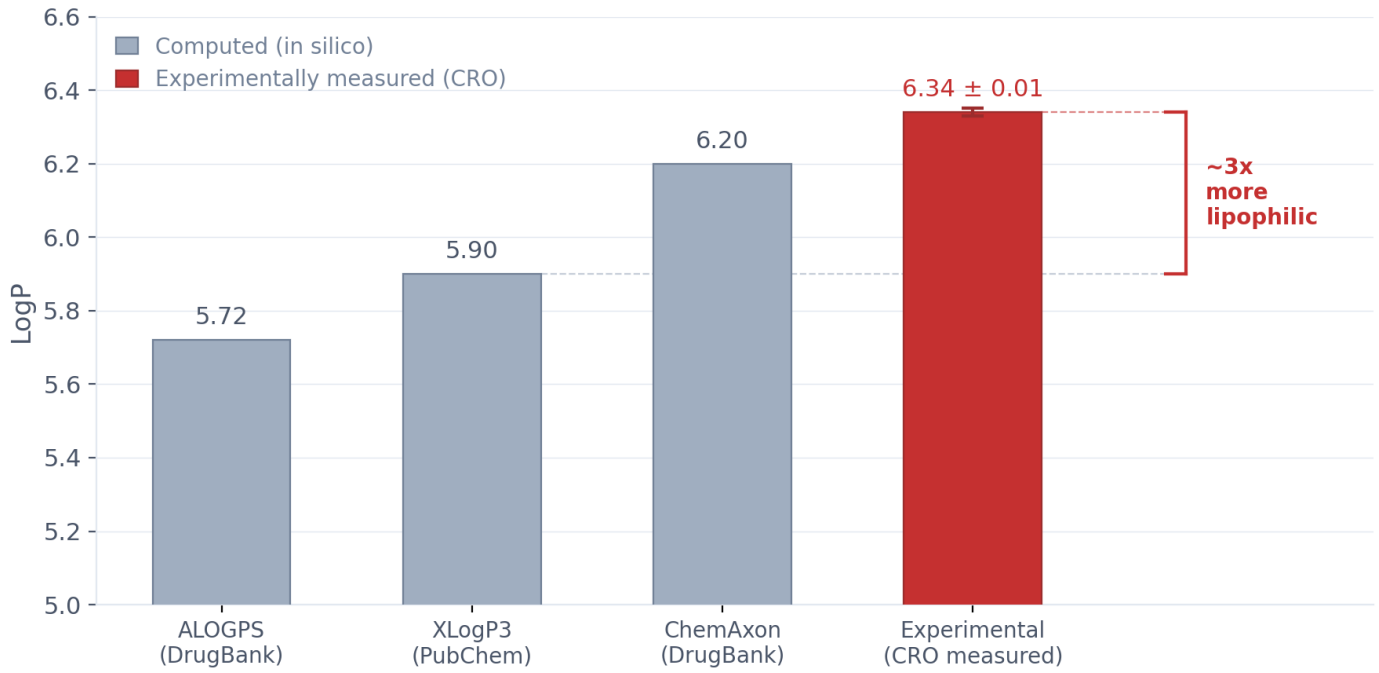
3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	338.71 g/mol	Computed by PubChem 2.2 (PubChem release 2025.09.15)
XLogP3-AA	5.9	Computed by XLogP3 3.0 (PubChem release 2025.09.15)

Experimentally-measured logP by our CRO (blinded) is 6.34, ~3X higher than the 5.9 computational logP predicted by molecular structure – unsurprising as computation underestimates if lipophilicity is this extreme

PubChem XLogP3 is the standard for computed logP and estimates 5.9 vs. experimentally-measured value of 6.34. As logP is on a logarithmic scale, the actual value is about 3X more lipophilic than the one predicted by its molecular structure – a typical result as computational methods tend to underestimate the logP for extremely lipophilic compounds.

Experimentally-measured logP vs. computed values - ~3X more lipophilic than predicted by the widely-trusted PubChem XLogP3 model



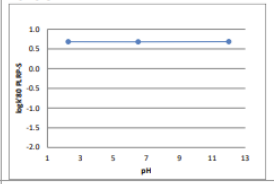
Source: https://go.drugbank.com/drugs/DB14828; https://pubchem.ncbi.nlm.nih.gov/compound/49846599; CRO analysis commissioned by Scorpion Capital

Obefazimod's lipophilicity is so extreme that measuring logP is notoriously difficult -- concentration is virtually undetectable in aqueous -- thus, we used an academic lab known for analysis of lipophilic drugs as our CRO

The university laboratory we contracted with is run by highly-published and cited scientists known for expertise in characterizing extremely lipophilic drugs whose logP is hard to measure by traditional methods. We sent them samples of obefazimod with 99.85% purity obtained from a well-known supplier of chemical compounds. The lab, serving as our CRO, analyzed the molecule on a blinded basis without information about its molecular structure. We have not disclosed the name of the compound to the lab.

Experimentally-measured logP result (CRO report excerpt) + HPLC/chromatographic protocol

Report template

Descriptor	Result
Molecular structure	Unknown
MW	Around 350
pK_a (potentiometric method)	No measurable pK_a within the pH range of 2–12. *Method: Dissociation constants were measured using a SiriusT3 instrument (Pion Inc., https://www.pion-inc.com/) equipped with a Ag/AgCl double junction reference pH electrode and a turbidity sensing device and the SiriusT3refine software (v. 2.0.12.0). Titration experiments were conducted in 0.15 M KCl solution under a nitrogen atmosphere at a temperature of 25 ± 1 °C. All tests were performed using standardized 0.5 M KOH and 0.5 M HCl as titration reagents. For all compounds, psKa values were determined in 30–50% MDM (20% ACN, 20% Dioxane, 20%MeOH).*
Assessment acidic/basic/neutral nature	Neutral compound (*method described in 0.1021/acs.molpharmaceut.5b00910*) RT: 3.00 (pH = 2.3); 3.02 (pH = 6.5); 2.93 (pH about 12.0) T0: 0.51 
logP (potentiometric method)	As no pK_a could be determined within the investigated range, no log P experiment could be performed.
BRlogP	6.34±0.01 (*method described in 10.4155/fdd-2019-0002*) RT: 6.35 (average of 6.31, 6.32, 6.43) T0: 0.50

Experimental lipophilicity for beyond Rule of 5 compounds

Aim: To set up a chromatographic strategy for the determination of log P for beyond Rule of 5 (bRo5) drugs. **Materials & methods:** Capacity factors measured by reverse phase-HPLC. Balance of intermolecular interactions governing systems assessed by partial least squares regression (PLSR) coupled with block relevance anaysis (PLSR-BR) and multiblock PLSR (MBPLSR). Determination of virtual log P obtained through conformational sampling. **Results:** log k'60 is highly correlated with log P for a dataset of 36 Ro5 compliant compounds (R^2 = 0.93, Q^2 = 0.90). We refer to the value generated via this method as BRlogP. The balance of intermolecular forces controlling BRlogP and log P are very similar. The ElogPs measured for the bRo5 dataset are significantly higher than corresponding BRlogP. **Conclusion:** The combination of BRlogP and ElogP provides an experimental lipophilicity range for bRo5 compounds.

LogP result 6.34 ± 0.01 and measurement method employed

Source: Report prepared by university lab serving as CRO on behalf of Scorpion Capital; https://www.tandfonline.com/doi/full/10.4155/fdd-2019-0002

Abivax has also never disclosed obefazimod's pK_a, to our knowledge – we asked the same university lab to experimentally measure its value, given the technical challenge due to its outlier lipophilicity -- protocol below

Measuring both logP and pK_a is challenging for highly lipophilic compounds. We reached out to this lab as it has developed highly-cited protocols as well as for its expertise with specialized instrumentation used in pharmaceutical R&D for profiling such molecules.

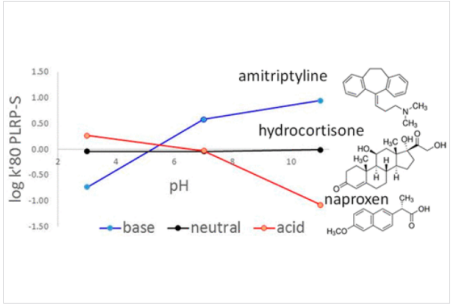
pK_a measurement – potentiometric protocol and equipment used

Report template

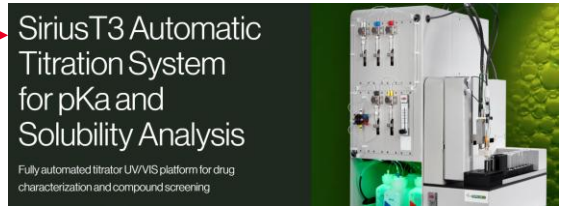
Descriptor	Result
Molecular structure	Unknown
MW	Around 350
pK_a (potentiometric method)	No measurable pK_a within the pH range of 2–12. *Method: Dissociation constants were measured using a SiriusT3 instrument (Pion Inc., https://www.pion-inc.com/) equipped with a Ag/AgCl double junction reference pH electrode and a turbidity sensing device and the SiriusT3refine software (v. 2.0.12.0). Titration experiments were conducted in 0.15 M KCl solution under a nitrogen atmosphere at a temperature of 25 ± 1 °C. All tests were performed using standardized 0.5 M KOH and 0.5 M HCl as titration reagents. For all compounds, pskа values were determined in 30–50% MDM (20% ACN, 20% Dioxane, 20%MeOH).*
Assessment acidic/basic/neutral nature	Neutral compound (*method described in 0.1021/acs.molpharmaceut.5b00910*) RT: 3.00 (pH = 2.3); 3.02 (pH = 6.5); 2.93 (pH about 12.0) T0: 0.51
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A Fast Chromatographic Method for Estimating Lipophilicity and Ionization in Nonpolar Membrane-Like Environment

Abstract



This study describes the design and implementation of a new chromatographic descriptor called log k'80 PLRP-S that provides information about the lipophilicity of drug molecules in the nonpolar environment, both in their neutral and ionized form. The log k'80 PLRP-S obtained on a polymeric column with acetonitrile/water mobile phase is shown to closely relate to log $P_{toluene}$ (toluene dielectric constant ε ~ 2). The main intermolecular interactions governing log k'80 PLRP-S were deconvoluted using the Block Relevance (BR) analysis. The information provided by this descriptor was compared to ElogD and *calc*log P_{tol}, and the differences are highlighted. The "charge-flush" concept is introduced to describe the sensitivity of log k'80 PLRP-S to the ionization state of compounds in the pH range 2 to 12. The ability of log k'80 PLRP-S to indicate the propensity of neutral molecules and monoanions to form Intramolecular Hydrogen Bonds (IMHBs) is proven through a number of examples.



Source: Report prepared by university lab serving as CRO on behalf of Scorpion Capital; https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.5b00910; https://www.pion-inc.com/solutions/products/siriust3

Obefazimod has no measurable pK_a across pH 2-12, per CRO results -- it is neutral, so its experimentally-measured logP of 6.34 is not lowered by ionization -- a devastating result that confirms its lipophilic liability

A drug with an ionizable group loses lipophilicity once pH crosses its pK_a and the molecule charges up. Obefazimod has no pK_a to cross: the CRO found no measurable pK_a anywhere in the physiological window (pH 2–12), and confirmed it by measuring lipophilicity at three pH points — 2.3, 6.5 and 12 — where the values were identical (the flat row in the table is the pH-independence screen, not the octanol–water logP). Because it never ionizes, its lipophilicity is the same in every compartment of the body. And that lipophilicity is extreme: an experimentally measured logP of 6.34 (BRlogP, chromatographic; replicates 6.31 / 6.32 / 6.43), corroborated by computational XLogP3 ≈ 5.9.

CRO results -- pK_a by potentiometric titration; logP by BRlogP (chromatographic)

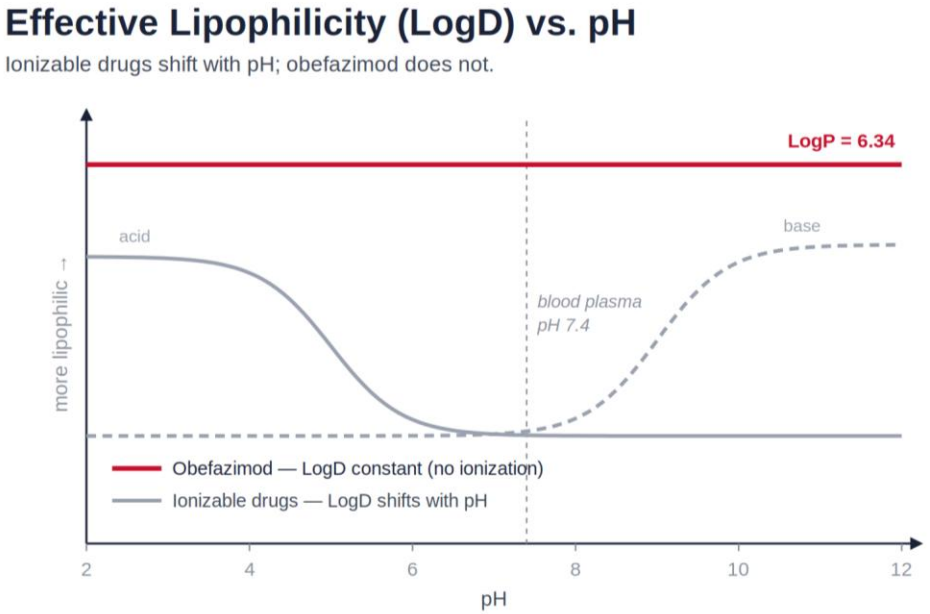
Report template

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logP (potentiometric method)	As no pK_a could be determined within the investigated range, no log P experiment could be performed
BRlogP	6.34±0.01 (*method described in 10.4155/fdd-2019-0002*) RT: 6.35 (average of 6.31, 6.32, 6.43) T0: 0.50

"No measurable pKa within the pH range of 2-12"

"Neutral compound"





Source: Report prepared by university lab serving as CRO on behalf of Scorpion Capital

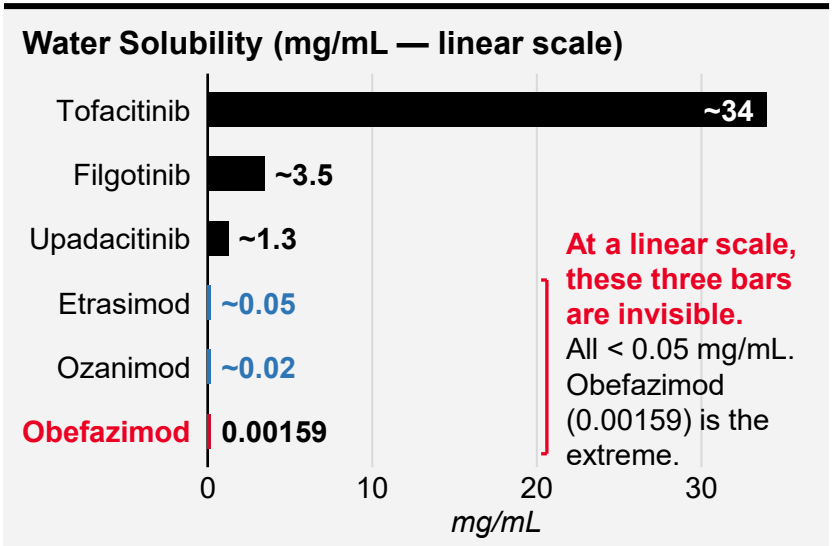
Obefazimod is essentially insoluble in water -- physical confirmation of extreme lipophilicity, and a dramatic solubility outlier vs. UC competitors

Obefazimod is essentially insoluble in water (0.00159 mg/mL) -- an independent physical confirmation of a LogP in the ~6 range, since high LogP and low aqueous solubility are two sides of the same coin. It is ~800–21,000× less soluble than the JAK inhibitors (≈21,000× vs. tofacitinib) and ~10–30× less soluble than the S1P modulators. Etrasimod is the control case: it is just as lipophilic (LogP ~6), yet ~30× more soluble -- because it is an ionizable carboxylic acid with a marketed salt form. Obefazimod is neutral across pH 2–12 – it has similar lipophilicity but no ionization and therefore no mitigant.

Water solubility of obefazimod vs. approved UC drugs

Drug	Class	LogP	Water Solubility
Tofacitinib	JAK (pan)	**1.5**	~34 mg/mL
Filgotinib	JAK1	**1.8**	~3.5 mg/mL
Upadacitinib	JAK1	**2.2**	~1.3 mg/mL
Ozanimod	S1P mod.	**3.7**	~0.02 mg/mL
Etrasimod	S1P mod.	**~6**	~0.05 mg/mL
Obefazimod	CBC20/80 (?)	**~6**	**0.00159 mg/mL**

Same LogP but 30× the solubility.
Etrasimod is an ionizable acid while obefazimod is neutral pH 2–12 with no pH-dependent rescue, thus remaining structurally insoluble



Other approved UC drugs dissolve readily in water, or can be made to - obefazimod cannot

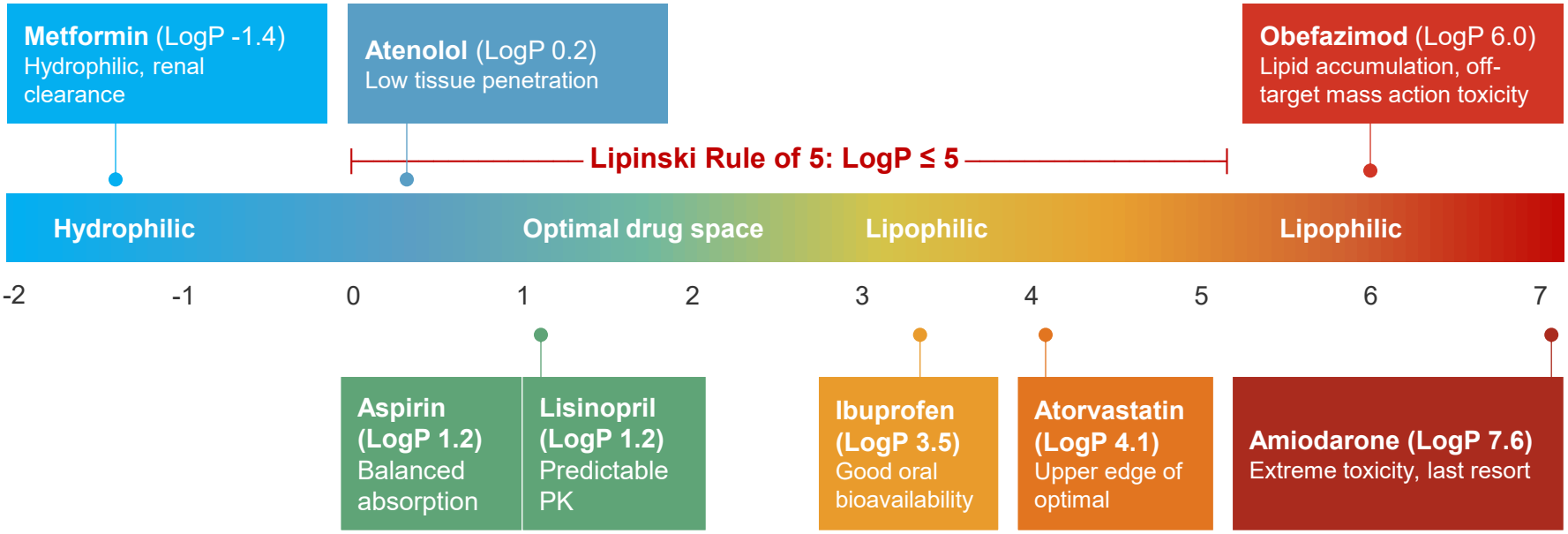
Source: Obefazimod solubility per DrugBank/ALOGPS https://go.drugbank.com/drugs/DB14828; LogP basis: PubChem XLogP3 (etrasimod 6.4); obefazimod ~6.34 measured (BRlogP chromatographic). Solubility: marketed salt at favorable pH for comparators (tofacitinib citrate, acidic pH); intrinsic for obefazimod (neutral).

Chapter 6. The drug's characteristics violate virtually all landmark drug-likeness screens/rules for viability and safety

Obefazimod's logP of ~6 far exceeds Lipinski's Rule of 5 -- a standard screen for oral drug viability and safety -- and the lipophilicity range of virtually all approved oral drugs, whether UC or not

Lipinski's Rule of 5 is the pharmaceutical industry's standard screen for oral drug viability. Named for its use of multiples of 5, it sets four thresholds: molecular weight ≤500, LogP ≤5, hydrogen bond donors ≤5, and acceptors ≤10. Compounds breaching two or more have poor absorption and bioavailability - most never reach patients. Of the four, LogP is the most consequential: it governs how a drug distributes between water (blood, GI fluid) and fat (cell membranes, tissue). Standard medicinal chemistry targets LogP between 1–4. Above 5, poor solubility, erratic absorption, high tissue accumulation, and off-target toxicity are a certainty. Obefazimod's LogP exceeds this limit by a full log unit, placing it far outside the range of virtually all approved oral drugs.

Lipophilicity spectrum (logP) – approved drugs by logP range



Source:

Obefazimod violates one of the industry's most basic screens for oral drug viability - a threshold exceeded only for life-saving drugs of last resort

~75% of approved oral drugs have LogP between 1–4. Only desperate-need drugs like amiodarone (life-threatening arrhythmias) tend to get approved above LogP 5.

Lipinski's Rule of 5 — the industry standard for oral drug viability

Molecular weight ≤ 500 Da	**LogP** ≤ 5	**H-bond donors** ≤ 5	**H-bond acceptors** ≤ 10

Compounds violating ≥2 rules have poor oral bioavailability. Obefazimod's LogP of ~6 violates the lipophilicity criterion by a full log unit.

Why LogP is the most consequential of the five parameters

Absorption	**Distribution**	**Toxicity**
LogP >5 compounds have poor aqueous solubility, leading to erratic GI absorption and high food-effect variability. Obefazimod's bioavailability is food-dependent.	Extreme lipophilicity drives massive tissue accumulation. A LogP 6 compound partitions 10^6:1 into lipid vs water. Plasma levels represent a tiny fraction of total body burden.	Tissue-trapped drug interacts with off-target membranes: hERG channels, mitochondrial membranes, lysosomal membranes. This drives the multi-organ toxicity seen with amiodarone — and now emerging with obefazimod.

What happens above LogP5

Unpredictable PK	**Tissue trapping**	**Off-target effects**
Long $t^{1/2}$, redistribution, variable exposure	Accumulates in fat, liver, membranes	hERG, phospholipidosis, lipid dysregulation

Textbook consensus: lipophilicity is THE primary physicochemical determinant of drug quality – seminal paper cited 3,000 times: "most important drug-like property"; drives off-target promiscuity and toxicity

Foundational Nature Reviews analysis: as lipophilicity rises, a molecule's tendency to hit unintended targets climbs sharply -- obefazimod sits past where almost every reference drug falls.

LogP vs. off-target promiscuity for >2,000 reference drugs and compounds – curve climbs steeply

The influence of drug-like concepts on decision-making in medicinal chemistry

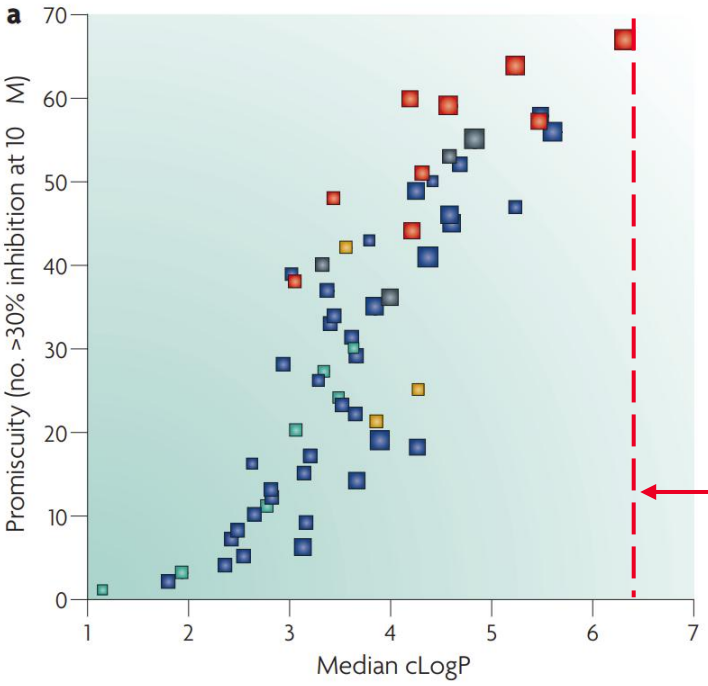


Figure 3(a) from paper: *off-target promiscuity vs. lipophilicity for 2,133 drugs and reference compounds across a 200-assay Cerep BioPrint panel.*

Promiscuity rises steeply and near-sigmoidally with cLogP (fit r = 0.83). Obefazimod's logP of 6.34 sits at the far-right, highest-risk end of the entire reference set

Obefazimod logP*

Source: https://pubmed.ncbi.nlm.nih.gov/17971784/ ; *dashed line in red ours for emphasis, approximate/estimation

Two key Pfizer papers -- cited 1,400 times in the literature -- quantify the danger via the 3/75 rule: drugs with both logP>3 and TPSA<75 are far more likely to be toxic – obefazimod logP 6.34 + TPSA 34 is deep in red alert zone

A Pfizer dataset of 245 compounds found that less polar, more lipophilic compounds had increased likelihood of toxic events, and critically that the trend held across a wide range of toxicity types and chemistry -- i.e., it's not mechanism-specific. A companion review paper indicated four drivers of toxicity: "primary pharmacology, off target pharmacology, the presence of a defined structural fragment that can be associated with adverse outcomes and the overall physicochemical properties of the molecule"; "2.5 times more likely to be toxic…an odds ratio of greater than 6…"

Two Pfizer papers – original paper (tables left) indicates sharply elevated toxicity + off-target promiscuity; companion review paper (charts right) indicate odds of toxicity climb steeply

Physiochemical drug properties associated with in vivo toxicological outcomes

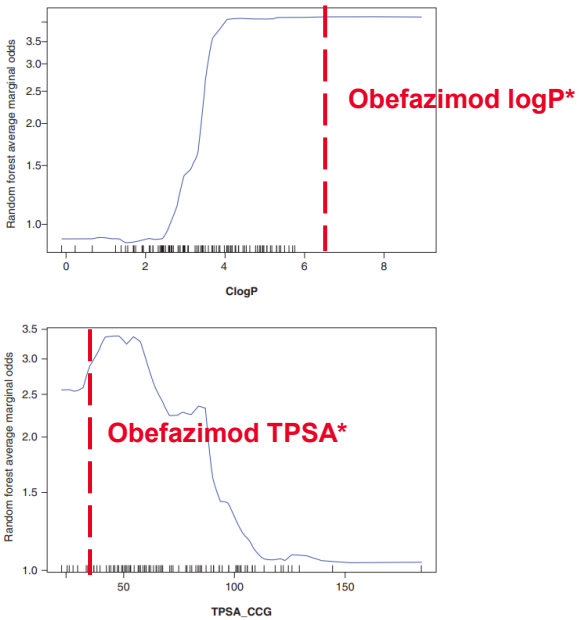
Physicochemical drug properties associated with in vivo toxicological outcomes: a review

Table 1
Observed odds for toxicity versus Clog*P*/TPSA

Toxicity	Total-drug		Free-drug	
	TPSA > 75	TPSA < 75	TPSA > 75	TPSA < 75
Clog*P* < 3	0.39 (57)	1.08 (27)	0.38 (44)	0.5 (27)
Clog*P* > 3	0.41 (38)	*2.4 (85)*	0.81 (29)	*2.59 (61)*

Table 2
Observed odds for promiscuity versus Clog*P*/TPSA

Promiscuity	TPSA > 75	TPSA < 75
Clog*P* < 3	0.25 (25)	0.80 (18)
Clog*P* > 3	0.44 (13)	*6.25 (29)*



Source: Obefazimod TPSA per PubChem https://pubchem.ncbi.nlm.nih.gov/compound/49846599#section=Computed-Properties; https://pubmed.ncbi.nlm.nih.gov/18691886/; https://www.tandfonline.com/doi/full/10.1517/17425250903042318?scroll=top&needAccess=true; *red ours for emphasis, dashed lines are estimation/approximate

ABX464 fails all nine fundamental drug-likeness screens below, including Pfizer's landmark 3/75 rule predicting toxicity, placing it in the highest-risk toxicity quadrant. Its logP 6.35 breaches every major lipophilicity limit.

Published between 1997 and 2010, various rules were derived by retrospective analysis of real compound sets to predict toxicity and ADME from physical parameters. Each arrived at the same conclusion: lipophilicity was the dominant predictor (higher = worse), and all set a ceiling for log P between 4 and 5.88. ABX464 exceeds every log P limit and falls in the toxic quadrant of Pfizer's 3/75 rule. No reasonable reading of these studies places ABX464 inside the drug-like space.

Rule	Limit	ABX464	Verdict	What the limit predicts
Lipinski Rule of Five, 1997	log P ≤ 5	**6.35**	**Violated**	Oral absorption and membrane permeability
Ghose, 1999	log P −0.4 to 5.6	**6.35**	**Violated**	Drug-like chemical space
Egan, 2000	log P ≤ 5.88 with TPSA ≤ 131.6 Å²	**6.35; 34.2 Å²**	**Violated log P**	Passive intestinal absorption
Muegge, 2001	log P −2 to 5	**6.35**	**Violated**	Pharmacophore-based drug-likeness
Gleeson 4/400, 2008	log P ≤ 4 and MW ≤ 400	**6.35; 338.7**	**Violated log P**	ADMET liability across assays
3/75 (Pfizer), 2008[1]	log P ≤ 3 or TPSA ≥ 75 Å²	**6.35; 34.2 Å²**	**Violated both**	6.2-fold higher in vivo toxicity across 245 preclinical programs
Johnson Golden Triangle, 2009	log D at pH 7.4 between −2 and 5, MW 200 to 500	**6.35 (log D = log P)**	**Violated log D**	Clearance and permeability optimized together
Waring, 2010	log P ≤ 4	**6.35**	**Violated**	Aqueous solubility becomes the limiting property
Baseline toxicity (narcosis) QSAR	validity to log P ≈ 6	**6.35**	**Violated**	Membrane burden reaches a lethal level below the solubility limit

[1]Pfizer 3/75 rule: A retrospective audit of Pfizer's in vivo toleration studies across 245 preclinical compounds found two properties predicted animal toxicity, calculated log P and topological polar surface area (TPSA, the surface contributed by nitrogen and oxygen atoms and their attached hydrogens), with cut points at 3 and 75 Å². ABX464 is in the highest incidence quadrant.

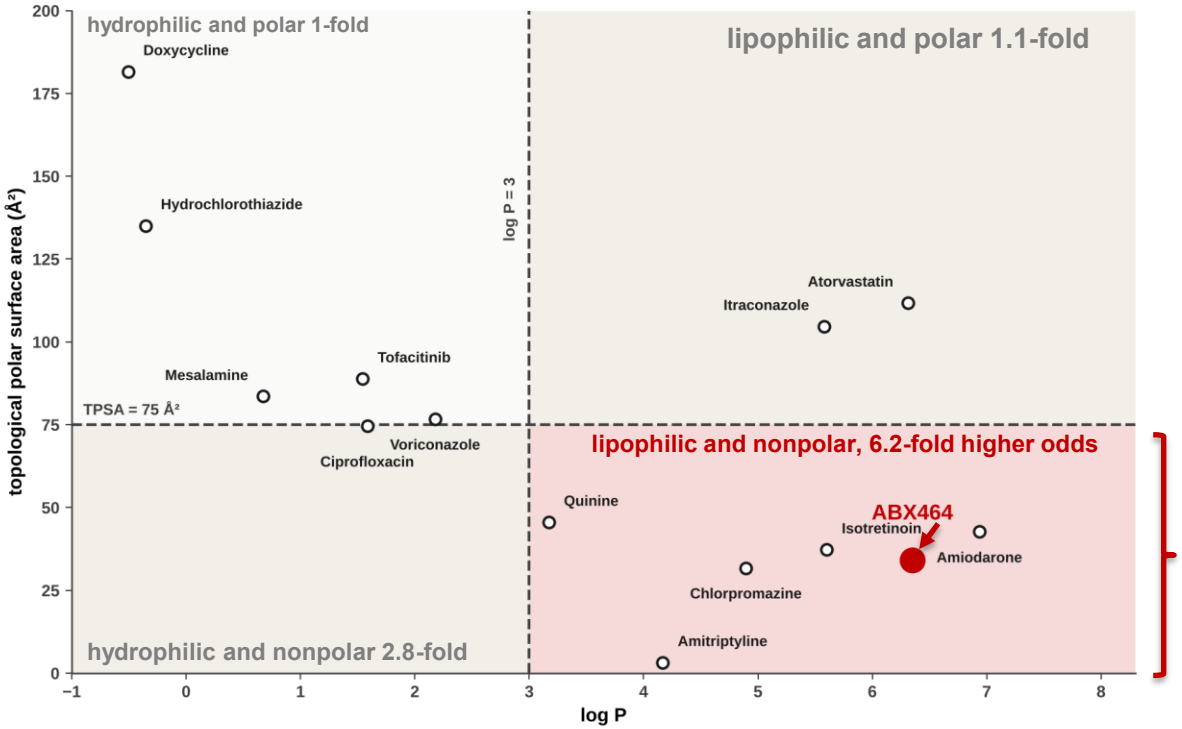
We measured log P 6.35 by reverse-phase HPLC under OECD Test Guideline 117. Topological polar surface area 34.2 Å² by the Ertl method. Molecular weight 338.7 g/mole.

Sources: Lipinski, Adv Drug Deliv Rev 1997;23:3-25; Ghose, J Comb Chem 1999;1:55-68; Egan, J Med Chem 2000;43:3867-3877; Muegge, J Med Chem 2001;44:1841-1846; Gleeson, J Med Chem 2008;51:817-834; Hughes, Bioorg Med Chem Lett 2008;18:4872-4875; Johnson, Bioorg Med Chem Lett 2009;19:5560-5564; Waring, Expert Opin Drug Discov 2010;5:235-248; Verhaar, Chemosphere 1992;25:471-491; Ertl, J Med Chem 2000;43:3714-3717; OECD Test Guideline 117; Scorpion Capital log P and pKa report and lab experiments; Scorpion Capital literature review, research, estimates, and analysis

Pfizer's 3/75 screen puts ABX464 in its highest-risk toxicity quadrant -- alongside a cluster of known photosensitizers

Pfizer 3/75 rule: Pfizer reports that drugs outside the 3/75 window, like ABX464, carry higher odds of an adverse finding than compounds inside it. ABX464 falls outside both thresholds with a strong margin (log P 6.35 vs 3, and TPSA 34.2 Å² vs 75). We used our measured log P (6.35) to put ABX464 on the 3/75 grid. Neighbors in that grid are all photosensitizers.

Compounds above logP 3 and below 75 Å² fall outside the preferred quadrant. ABX464 falls into the toxic quadrant.



Quadrant boundaries and toxicity ratios from Hughes 2008[1]. Comparator positions calculated from structure (Crippen log P, Ertl TPSA). ABX464 plotted at measured log P 6.35

Drugs in the toxic quadrant are all phototoxins

- **All five compounds are photosensitizers like ABX464.**
- **Isotretinoin (neutral) carries a photosensitivity warning.**
- **Quinine (neutral) shows phototoxicity and photoallergic reactions.**
- **Quinine and ABX464 are both quinolines (fused bicyclic aromatic scaffolds with photosensitive chromophores on their quinoline rings). ABX464 absorbs strongly at wavelengths that penetrate to basal keratinocytes where skin cancer originates.**

[1]Hughes 2008 audited Pfizer's in vivo toleration studies across 245 preclinical programs at Cmax below 10 µM. Compounds flagging both properties (calculated log P above 3, TPSA below 75 Å²) showed adverse-finding odds of 2.4 against 0.39 for compounds flagging neither, an odds ratio of 6.2. The quadrant values on the plot are those odds normalized to the reference quadrant.

Sources: Hughes, Bioorg Med Chem Lett 2008;18:4872-4875; Price et al., Future Med Chem review of the Pfizer dataset; Scorpion Capital literature review, research, estimates, and analysis

LogP driving toxicity is common knowledge -- Pfizer conclusion supported by Takeda, AstraZeneca, AbbVie, and Eli Lilly papers analyzing their own drug datasets; "role of lipophilicity…is of paramount importance"

Lipophilicity is one of the most validated predictors of ADMET failure: across Pfizer, Takeda, AstraZeneca, AbbVie, and Lilly datasets, higher LogP is consistently linked to worse clearance, distribution, off-target toxicity, and lower developability. ABVX's chronic dosing of a LogP ~6 compound sits far outside the normal range for approved oral drugs and makes its AE pattern highly predictable.

Representative papers on key role of lipophilicity in driving ADMET and toxicity

Lipophilicity in drug discovery

Importance of the field: The role of lipophilicity in determining the overall quality of candidate drug molecules is of paramount importance. Recent developments suggest that, as well as determining pre-clinical ADMET (absorption, distribution, metabolism, elimination and toxicology) properties, compounds of optimal lipophilicity might have increased chances of success in development.

Lipophilic Efficiency: The Most Important Efficiency Metric in Medicinal Chemistry

Lipophilicity and biomimetic properties to support drug discovery

Takeda paper

Utility of Physicochemical Properties for the Prediction of Toxicological Outcomes: Takeda Perspective

AbbVie paper

Toxicology Strategies for Drug Discovery: Present and Future

Lower logP leads to better ADMET across the board

Generation of a set of simple, interpretable ADMET rules of thumb

Probing the links between in vitro potency, ADMET and physicochemical parameters

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC7025387/; https://pubmed.ncbi.nlm.nih.gov/26588328/; https://pubmed.ncbi.nlm.nih.gov/18232648/; https://pubmed.ncbi.nlm.nih.gov/21358739/; https://pubmed.ncbi.nlm.nih.gov/28644732/; https://www.tandfonline.com/doi/full/10.4155/fmc.12.208; https://pubmed.ncbi.nlm.nih.gov/22823020/

Lipophilicity drives multiple, independent toxicity mechanisms – linear relationship with off-target binding and promiscuity: phospholipidosis, mitochondrial toxicity, hERG liability and cardiotoxicity, liver injury

High lipophilicity does not create one isolated risk -- it amplifies broad target promiscuity and multiple toxicity pathways at once. At LogP ~6, obefazimod is at the extreme tail where pharma datasets show sharply rising off-target binding, phospholipidosis, hERG liability, cardiotoxicity, and liver injury risk.

Lipophilicity is key driver of promiscuity and off-target behavior – quantified by various studies

Contributions of molecular properties to drug promiscuity

Modeling Promiscuity Based on in vitro Safety Pharmacology Profiling Data

Physicochemical drug properties associated with *in vivo* toxicological outcomes: a review

Obefazimod logP of 6 sits in extreme territory

Same paper cites ~dozen studies by large pharma cos quantifying lipophilicity vs. promiscuity

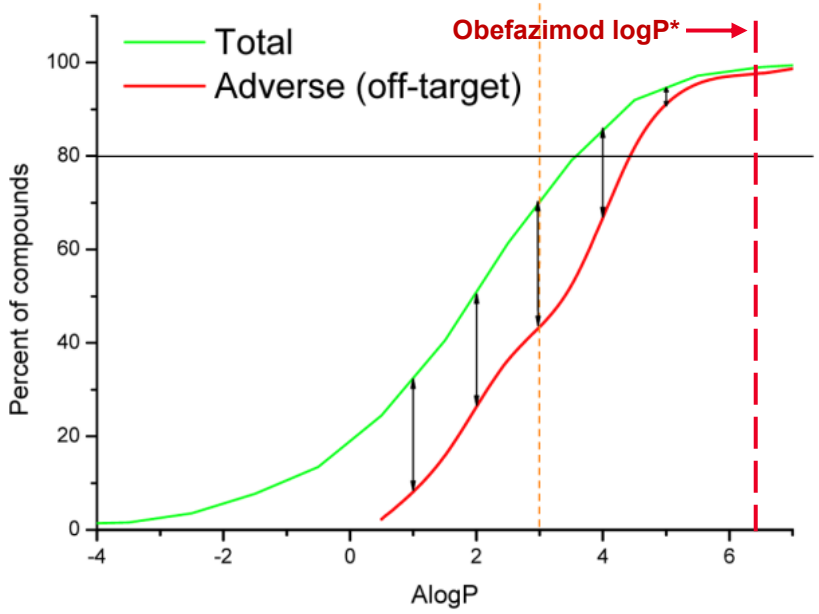


Table 1. Promiscuity–Property Relationships Reported by Different Organizations

organization	no. of compounds	no. of assays	physicochemical properties investigated	dependency on physicochemical properties	ref
Pfizer	75 000 in-house	220 in-house	MW, log *P*	MW: negative log *P*: positive	27
Pfizer	1098 drugs and 430 project compounds	70 Cerep BioPrint panel	log *P*	log *P*: positive	27
Pfizer	108 clinical candidates	48 Cerep BioPrint panel	log *P*, TPSA	log *P*: positive TPSA: negative	18
Organon	138 in-house	Promiscuity is defined as low selectivity.	MW, log *P*	MW: negative log *P*: positive	28
Novartis	3138 in house	50–79 in-house	MW, AlogP, HBA, HBD, #o, #N, RotB, #rings, ring assemblies, terminal rotamers, chain assemblies	MW: positive log *P*: positive	23
AstraZeneca	2133 drugs and ref compounds	200 Cerep	MW, clogP, pK_a, #rings	MW: positive log *P*: positive pK_a: positive for bases	2
Roche	213 in-house	80 Cerep	in silico: MW, Nhev, HBD, HBA, RotB, #rings, #Ar rings, #non-Ar rings, PSA, clogP, amphiphilicity, pK_a, ionization state, clogD measured: solubility, log *D*(7.4), permeability, pK_a	MW: no log *P*: positive pK_a: positive for bases	29
AstraZeneca	2267 drugs and ref compounds	200 Cerep BioPrint panel	Nhev, clogP, and molecular framework (f_{MF})	Nhev: bell shaped log *P*: positive	30
ChEMBL	40 408 literature	>500 literature	MW, log *P*, pK_a	MW: positive log *P*: positive pK_a: positive for neutrals and bases	6
GSK	>2500 drugs and in-house	>490 in-house	Chrom log *P* and #Ar	log *P* + #Ar: positive	31
Roche	2413 drugs and druglike compounds	141 safety-relevant targets	MW, clogp, pK_a, HBA, HBD, #Ar, PSA, RotB	log *P*: positive pK_a: positive for bases	32
Novartis	656 drugs	73 in-house	log *P*, pK_a	log *P*: positive pK_a: positive for neutrals and bases	33

Source:https://pubmed.ncbi.nlm.nih.gov/18691886/; https://pubmed.ncbi.nlm.nih.gov/23356819/; https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cmdc.200700036; *red ours for emphasis, dashed lines are estimation/approximate

Extensive literature on lipophilicity predicting drug failure and toxicity, particularly liver damage and cardiotoxicity/hERG liability

The literature highlights not just the broad promiscuity of lipophilic drugs, but the clinical consequences tied to their chemistry: DILI, hERG liability, cardiotoxicity, and ADMET failure. Obefazimod's LogP ~6 profile places it squarely in this risk zone — a profound mismatch for chronic ulcerative colitis therapy.

Peer-reviewed literature links high lipophilicity to the clinical liabilities that most frequently derail chronic oral drugs: DILI (drug induced liver injury) and hERG/cardiac risk

Is there enough focus on lipophilicity in drug discovery?

Source: https://www.tandfonline.com/doi/full/10.1080/17460441.2020.1691995#d1e114

High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury

Source: https://pubmed.ncbi.nlm.nih.gov/23258593/

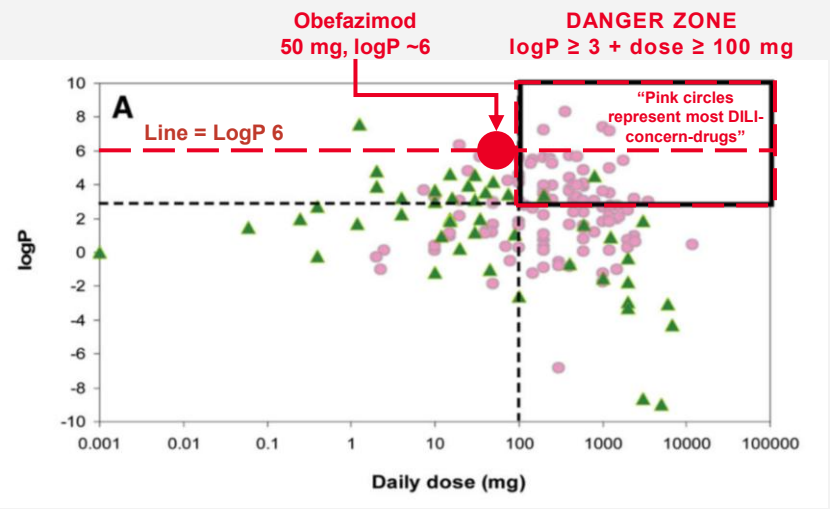
A quantitative assessment of hERG liability as a function of lipophilicity

Source: https://pubmed.ncbi.nlm.nih.gov/17239590/

FDA toxicology group's landmark 'rule-of-two' paper: high lipophilicity + high dose = liver damage. 14 of 15 rule-positives were withdrawn for hepatotoxicity -- ominous for obefazimod's logP 6 chronic daily dosing.

Chen et all (Hepatology, 2013) "rule of two" is a seminal paper on hepatotoxicity -- published by the FDA's National Center for Toxicological Research and ranked #3 in the list of "top 15 most-cited" liver toxicity publications. It found that drugs dosed at ≥100 mg/day with logP ≥3 carry 14X elevated odds of drug-induced liver injury. Obefazimod's 50mg daily dose technically sits below the 100mg threshold - but the dose offset is meaningless when lipophilicity is this extreme.

Rule-of-two danger zone (Chen et al. 2013, Fig. 1A) -- obefazimod sits at the boundary; every drug shown with similar logP > 6 is associated with liver injury, except for one dosed at only ~1mg/day



Why obefazimod sub-100mg dose offers no real safety margin at logP 6

1. **Obefazimod is 1,000× more lipophilic than the rule's threshold.** The rule was built around logP ≥3. Obefazimod is at logP 6 -- three log units above the cutoff, deep in territory the model wasn't designed to evaluate. Near-complete plasma protein binding, massive volume of distribution, phospholipidosis risk, and hERG channel liability that has driven numerous market withdrawals.

2. **Multiple toxicity mechanisms scale with logP independent of dose.** Off-target promiscuity peaks at clogP >2.5–3 -- obefazimod is at 6. Reactive metabolite formation correlates with logP across both Pfizer's and Roche's compound databases. Lower the dose all you want — these mechanisms don't care.

3. **Chronic UC dosing turns tissue accumulation into a time bomb.** UC patients stay on therapy for years or decades. A logP 6 compound dosed daily and indefinitely accumulates in liver, adipose, and cell membranes far beyond what plasma Cmax suggests. Cisapride (logP 3.9) at only 10–20 mg QID killed people via QTc prolongation after chronic use — obefazimod's lipophilicity is two log units higher.

4. **The 100 mg threshold is a statistical artifact.** Authors explicitly state the rule cannot grade DILI severity; follow-up DILI score models incorporating reactive metabolites have lowered the dose-of-concern threshold closer to 50 mg. Obefazimod sits exactly where newer models begin flagging risk.

Source: https://pubmed.ncbi.nlm.nih.gov/23258593/

Cardiotoxicity via hERG liability is a class property of lipophilic drugs, near-certainty at logP ~6. Cisparide FDA precedent -- withdrew a chronic GI drug, despite low daily dose. Obefazimod is >100X more lipophilic + higher dose.

Cisapride was a chronic GI drug withdrawn for fatal cardiac events at LogP ~3.9. Obefazimod targets the GI system at LogP ~6, 100x more lipophilic. Waring and Johnstone (2007) is a seminal, highly-cited paper using AstraZeneca data (validated on ~6,000 compounds) that shows that hERG potency scales with lipophilicity/logP as a continuous function. The hERG channel's inner cavity is large and lined with hydrophobic pockets that preferentially bind lipophilic molecules -- the more lipophilic the compound, the stronger the binding. The model was never validated at LogP ~6 given the rarity of drugs this lipophilic – the Waring regression curve asymptotes and the model predicts near-certain hERG liability at this logP.

Seminal, highly-cited paper: logP is the main driver of increasing hERG potency, Waring and Johnstone, 2007

A quantitative assessment of hERG liability as a function of lipophilicity

Michael J. Waring* and Craig Johnstone

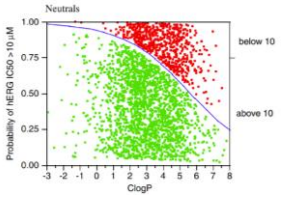
AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Received 26 September 2006; revised 15 December 2006; accepted 16 December 2006
Available online 22 December 2006

Abstract—The impact of lipophilicity as a factor contributing to hERG potency is assessed for a large dataset of compounds of differing ionisation type. This dataset is derived from compounds tested in the Ionworks™-based in vitro electrophysiology hERG assay at AstraZeneca. Using logistic regression, a quantification of the risk associated with increasing lipophilicity is presented. The anticipated differences between acidic, basic and neutral compounds are apparent in the data but lipophilicity is shown to be a stronger driver for hERG potency than might have been expected. Simple rules defining target lipophilicity values for minimizing hERG liability are derived.
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Table 5. Target upper limits of log *D* and clog *P* to ensure >70% of compounds achieve a hERG IC_{50} of greater than 10 μM

	Acids	Bases	Neutrals	Zwitterions
log *D*	>4	1.4	3.3	2.3
clog *P*	>9	1.9	4.0	4.4



WHAT THE MODEL PREDICTS

- **Waring & Johnstone (2007)**
  AstraZeneca IonWorks dataset
- The logistic regression shows hERG potency increases **continuously** with LogP. No safe cutoff exists.
- **At LogP ~6:**
  The curve has asymptoted. Predicted probability of potent hERG blockade approaches the ceiling for all ionization classes — basic, neutral, and acidic.
- The model was calibrated on LogP 0–5. Obefazimod at ~6 is beyond the training range — the prediction is extrapolation, but the direction is unambiguous.
- **Practical rule:** LogP < ~3 for bases, < ~4 for neutrals, to have reasonable hERG selectivity.

CISAPRIDE – CANARY IN THE COAL MINE

- Cisapride's deaths were primarily a CYP3A4 drug-interaction story. Co-administered inhibitors caused plasma spikes that pushed hERG blockade to lethal levels.
- **However, the underlying vulnerability was hERG.**
  Cisapride was a moderate hERG blocker at therapeutic concentrations. Its LogP ~3.9 facilitated both CYP3A4 substrate affinity and hERG channel access.
- **The regulatory lesson:**
  The FDA pulled a chronic GI drug because hERG liability — amplified by pharmacokinetic factors — killed patients. **Obefazimod's LogP ~6 means higher baseline hERG risk before any drug interactions are even considered.**

Source: https://pubmed.ncbi.nlm.nih.gov/17239590/#:~:text=Abstract,Potassium%20Channel%20Blockers

Chapter 7. Obefazimod's lipophilic liability is virtually unprecedented among FDA-approved drugs and within UC comparators specifically

Obefazimod's lipophilic liability is an outlier even among FDA-withdrawn high-logP drugs -- a graveyard of hepatic, cardiac, stroke, and other AE's

The pattern is stark. Among 15 "rule-of-two" positives in the FDA paper, 14 drugs were withdrawn hepatotoxic drugs. High risk for hepatotoxicity was observed with an odds ratio of 14.05 ($p < 0.001$). The table of withdrawn drugs indicates that high logP is a graveyard across mechanisms

FDA-withdrawn small molecules with LogP >3 versus obefazimod (~6.0) -- the class is graveyard with obefazimod's lipophilicity sitting near the top of the list

Drug	LogP	Indication	Withdrawn	Reason for Withdrawal
Halofantrine	**6.5**	Antimalarial	Restricted	*Fatal QTc prolongation*
Terfenadine	**6.5**	Antihistamine	1998	*Torsades de Pointes, sudden death*
Obefazimod	**6.0**	UC (IBD)	—	**IN DEVELOPMENT**
Astemizole	**5.6**	Antihistamine	1999	*Torsades de Pointes, sudden death*
Sibutramine	**5.2**	Obesity	2010	*CV events (stroke, MI)*
Grepafloxacin	**5.1**	Antibiotic	1999	*Fatal QTc prolongation*
Ticrynafen	**4.7**	Diuretic	1982	*Hepatotoxicity, deaths*
Cerivastatin	**4.3**	Statin	2001	*Fatal rhabdomyolysis*
Troglitazone	**4.2**	Diabetes	2000	*Liver failure, deaths*
Mibefradil	**4.2**	Cardiovascular	1998	*Fatal drug interactions*
Cisapride	**3.9**	GI (prokinetic)	2000	*Torsades de Pointes, deaths*
Benoxaprofen	**3.7**	NSAID	1982	*Hepatotox, fatal in elderly*
Rofecoxib	**3.5**	NSAID	2004	*CV events (MI, stroke)*

THE PATTERN

- **12 of 12 withdrawn drugs** on this list had LogP ≥ 3.5
- **Primary failure modes:**
  - QTc / cardiac death (6 drugs)
  - Hepatotoxicity (4 drugs)
  - CV events (2 drugs)
- Lipophilicity drives both Herg liability and hepatic accumulation

GI PRECEDENT: CISAPRIDE

- Cisapride was a **chronic GI drug** withdrawn for fatal cardiac eventsat LogP ~3.9, dosed 10–20mg QID
- **Obefazimod is 100x more lipophilic** targeting the same organ system.

Source: ; https://pubmed.ncbi.nlm.nih.gov/23258593/ FDA 21 CFR 216.24, GAO-01-286R, PubChem, DrugBank. LogP values are consensus experimental / predicted.

Almost no FDA precedent for a small molecule at logP > 6 chronically dosed at high mg. The few that exist are flops or orphan, oncology, or niche drugs with boxed warnings, heavy monitoring, high toxicity, or FDA withdrawal.

The thin cohort of FDA-approved, lipophilic small-molecule drugs reads as a liability catalogue -- none is a clean, convenient maintenance therapy. Clofazimine is the textbook tissue-storage drug -- red-brown skin/conjunctival discoloration and crystalline deposition in adipose. The one drug matching obefazimod on logP and dose – acitretin at 25-50mg – has a 4-month terminal half-life due to fat storage and is Pregnancy Category X with a multi-year post-treatment conception ban, resulting in a $37MM global market. And the FDA has issued safety alerts and pushed for withdrawal of avacopan for fatal liver injury.

High LogP small-molecule drugs dosed daily

Drug	Indication	Dose / day	Boxed warning	Monitoring burden
Acitretin logP ~6.1	Severe plaque psoriasis	**25–50 mg**	Teratogenicity (Preg. Cat. X); hepatotoxicity; alcohol prohibited	Two-form contraception + serial pregnancy tests; no blood donation 3 yrs; LFTs, lipids
Tamoxifen logP ~6.3	Breast cancer (treatment + prevention)	**20 mg**	Endometrial cancer / uterine sarcoma; stroke; pulmonary embolism	Gynecologic exams; thromboembolism watch; periodic CBC
Clofazimine logP ~7.7	Leprosy (orphan); NTM off-label	**50–100 mg**	Not boxed — crystalline GI deposition → bowel obstruction, splenic infarction, death	GI / skin surveillance; skin discoloration near-universal. U.S. expanded-access only since 2004
Avacopan logP ~7.5†	ANCA-associated vasculitis (adjunctive)	**30 mg BID (60 mg)**	Not boxed — hepatotoxicity; FDA 3/2026 alert (fatal DILI, VBDS); withdrawal proposed	Baseline + periodic liver function tests
Cinacalcet logP ~6.1	2° hyperparathyroidism (dialysis); parathyroid-ca hypercalcemia	**30 → 180 mg**	Not boxed — hypocalcemia; seizures	Serum calcium (monthly), phosphorus, iPTH
Raloxifene logP ~6.1	Postmenopausal osteoporosis; breast-cancer risk reduction	**60 mg**	Venous thromboembolism (DVT / PE); death from stroke	Thromboembolism watch; uterine / lipid monitoring
Toremifene logP ~7.2	Metastatic breast cancer	**60 mg**	QT prolongation	ECG, electrolytes (K / Mg), CBC, liver function

Source: logP values are calculated; standardize to one source (e.g., PubChem XLogP3) before publication. All listed drugs are ionizable (acid or base), so log $D_{7.4}$ runs 1–2+ log units below logP. †Avacopan logP to be confirmed. By contrast, obefazimod (logP ≈ 6.34) is permanently neutral across pH 2–12 — log D = logP, no ionization rescue — dosed 25–50 mg once daily.

Avacopan – one of only two neutral + extreme-logP comparators, acquired by Amgen for $4B in 2022 – is a disaster. In Apr ‘26, the FDA proposed to rescind approval due to liver injury and issues with the trial and NDA. The other comparator was pulled in ’95 – lipophilicity is the root of their toxicity.

Six of the seven comparators on the previous page are ionizable -- five weak bases and one acid -- meaning their "high logP" overstates how lipophilic they are in plasma; each gets a 1–2+ log-unit ionization rescue and travels as a far less lipophilic charged species. Avacopan is the one exception as it is neutral at physiological pH. The only commercially successful high LogP + neutral molecules we see are CFTR modulators for cystic fibrosis. However, their logP values are 3-5, making obefazimod >10-1000x more lipophilic at 6.34. Moreover, they are reserved for a fatal orphan indication and carry severe boxed warnings for drug-induced liver injury and liver failure, with onerous monitoring requirements.

Neutral (log D = logP) high-logP chronic oral drugs – the very small set

Drug	Ionizable group	Charge at pH 7.4	log $D_{7.4}$ vs logP
NEUTRAL · log D = logP — no ionization rescue			
Obefazimod logP ~6.34	None across pH 2–12 — permanently neutral	**neutral**	**log D = logP**
Avacopan logP ~7.5†	Only a weak arylamine (pKa ~4–5); piperidine N acylated (amide)	**essentially neutral**	**log D ≈ logP**
Probucol logP ~10	Bis-phenol (pKa ~10–11); no basic center	**neutral**	**log D ≈ logP**
IONIZABLE · log D < logP — effective lipophilicity rescued by charge			
Acitretin logP ~6.1	Carboxylic acid (pKa ~4.8)	anion	log D ≪ logP (~−2.6)
Tamoxifen logP ~6.3	Tertiary amine (pKa ~8.8)	cation	log D < logP
Clofazimine logP ~7.7	Imino base (pKa ~8.5)	partial cation	log D < logP
Cinacalcet logP ~6.1	2° aliphatic amine (pKa ~8.5)	cation	log D < logP
Raloxifene logP ~6.1	Piperidine base (pKa ~8–9) + 2 phenols	cation / amphoteric	log D < logP
Toremifene logP ~7.2	Tertiary amine (pKa ~8.8)	cation	log D < logP

Only two neutrral, extreme-logP comparators that we see

Obefazimod -- ???

Avacopan -- under threat of FDA withdrawal

Probucal -- withdrawn

The other extreme-logP comparators are ionizable, which means they are less lipophilic than their logP would otherwise indicate

†Avacopan neutrality is structure-based; probucol logP is calculated (~10); acitretin log D reflects near-complete ionization at pH 7.4. logP values are calculated.

Avacopan and obefazimod are both lipophilic, neutral, low TPSA. The FDA's withdrawal effort and journal retractions are typical for this tiny comparator set – a graveyard which violates basic drug rules like Lipinski, 3/75, Rule of Two and is littered with recalls or launch flops like propucal and etrasimod.

Avacopan (TAVNEOS) – recent press and controversy

CDER proposes to withdraw approval of TAVNEOS

NEJM Retracts Pivotal Trial of FDA-Approved Drug

— Move follows actions "inconsistent with proper research conduct," journal says

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Amgen's Tavneos faces withdrawal after FDA probe flags data tampering

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FDA Warns of Serious Liver Injury Risks From Vasculitis Drug Tavneos

Source: https://www.fda.gov/drugs/drug-alerts-and-statements/cder-proposes-withdraw-approval-tavneos; https://www.reuters.com/legal/litigation/medical-journal-retracts-paper-amgens-tavneos-drug-trial-after-fda-findings-2026-06-29/; https://firstwordpharma.com/story/7231776; https://www.webmd.com/drugs/updates/fda-warning-vasculitis-drug-tavneos-serious-liver-injury-risks

Two recent big pharma acquisition blunders both involved high-logP drugs – will a third acquirer be this dumb? Amgen blew $4B for Chemocentryx's avocopan; Pfizer torched $7B on Arena's UC drug etrasimod – a rapid launch flop and impairment -- with similar logP + TPSA profile as ABX464.

The track record of recent big pharma acquisitions involving high logP drugs indicates the challenges with obefazimod's profile.

Avacopan/Chemocentryx and Esrasimod/Arena Pharmaceuticals – acquisitions and drug issues

ChemoCentryx Data Fraud Allegations Surface

Updated: FDA claims trial 'manipulation' tainted approval of ChemoCentryx drug now owned by Amgen

Controversial drug at center of multibillion-dollar Amgen deal faces more questions after paper retracted

Pfizer bets on Arena's promising bowel disease treatment in $6.7 bln deal

"(Etrasimod) has the potential to be best-in-class drug in these indications...could be a multi-billion blockbuster drug in just Crohn's and ulcerative colitis and we forecast risk adjusted revenue of $3.8 billion."

Pfizer Takes Impairment Charges On Velsipity And Prevnar 13

"(Etrasimod) has the potential to be best-in-class drug in these indications...could be a multi-billion blockbuster drug in just Crohn's and ulcerative colitis and we forecast risk adjusted revenue of $3.8 billion…"

Source: https://www.bizjournals.com/sanfrancisco/news/2026/07/01/amgen-drug-deaths-vasculitis-tavneos-chemocentryx.html; https://www.startuphub.ai/ai-news/technology/2026/chemocentryx-data-fraud-allegations-surface; https://endpoints.news/fda-claims-trial-manipulation-tainted-approval-of-chemocentryx-drug/; https://insights.citeline.com/SC149711/Pfizer-Takes-Impairment-Charges-On-Velsipity-And-Prevnar-13/; https://www.reuters.com/markets/deals/pfizer-acquire-arena-pharmaceuticals-67-bln-deal-2021-12-13/

We count 1,200 NDA approvals in the last decade and only 18 at LogP ≥ 6 – each has a mitigant except obefazimod – which is an even more extreme outlier as it's neutral + low TPSA, further magnifying the safety hazard

We count about 1,200 NDA's approved by the FDA in the last decade (2016-2025), of which ~250 are small molecules with logP data we could pull – a mere18 sit at LogP ≥ 6. Eech carries a mitigant, unlike obefazimod -- cancer-grade risk-benefit, REMS, gut-restriction by design, short-duration regimen, or topical-only. We see no approval precedent even within this small logP >6 set in terms of dose × lipophilicity × duration. The others tare either pulse-dosed (HCV regimens are 8–12 weeks), gut-restricted (Bylvay, Livmarli, Ibsrela), or have dosing/exposure profiles that mitigate tissue accumulation.

Every approved small molecule drug at LogP ≥ 6 has a structural mitigant – obefazimod has none

Drug	LogP	Indication / setting	Mitigant	Why not a precedent for obefazimod
Obefazimod	**~6.0**	Ulcerative colitis (UC)		**Daily oral, chronic, non-fatl disease**
Venetoclax	**8.0**	CLL / AML	**Cancer + REMS**	*Black box: tumor lysis syndrome; mandatory 5-week ramp-up with inpatient TLS labs*
Triheptanoin	**7.7**	LCFAOD	**Lipid by design**	*Literally a triglyceride — lipophilicity is the mechanism, not a side effect*
Pibrentasvir	**7.5**	HCV (in Mavyret)	**Finite cure**	*8–12 week curative regimen — total exposure measured in weeks, not decades*
Avatrombopag	**7.2**	Thrombocytopenia	**Short-course**	*5-day course before procedures; chronic ITP use is intermittent and monitored*
Oteseconazole	**7.2**	Recurrent VVC	**REMS**	*REMS for embryofetal toxicity; women of non-reproductive potential only; t½ ~138d*
Tenapanor	**7.1**	IBS-C, hyperphosphatemia	**Gut-restricted**	*<0.5% systemically absorbed — LogP irrelevant to tissue exposure*
Elbasvir	**7.0**	HCV (in Zepatier)	**Finite cure**	*12-week curative HCV regimen — finite exposure window, not chronic suppression*
Trifarotene	**6.8**	Acne	**Topical**	*Topical cream — no meaningful systemic exposure regardless of LogP*
Lonafarnib	**6.5**	Hutchinson-Gilford progeria	**Ultra-rare fatal**	*Fatal pediatric disease (~400 patients globally); cancer-grade risk-benefit acceptable*
Odevixibat	**6.5**	Pediatric cholestasis	**Gut-restricted**	*Ileal bile acid transporter inhibitor; minimal systemic absorption by design*
Lotilaner	**6.5**	Demodex blepharitis	**Topical-like**	*Eyelid administration; targeted ectoparasite mechanism, minimal systemic exposure*
Bempedoic acid	**6.4**	Hypercholesterolemia	**Liver-localized**	*Prodrug requiring ACSVL1 (liver-restricted enzyme); active form is hepatic-localized*
Maralixibat	**6.4**	Pediatric cholestasis	**Gut-restricted**	*Ileal bile acid transporter inhibitor; gut-restricted by design*
Avacopan	**6.4**	ANCA vasculitis	**Black box + monitored**	*Black box: hepatotoxicity; rare disease; mandatory LFT monitoring*
Palovarotene	**6.2**	FOP	**REMS, ultra-rare**	*Fibrodysplasia ossificans progressiva (~800 patients globally); REMS program*
Siponimod	**6.1**	Secondary progressive MS	**Progressive disease**	*Progressive neurologic disease; first-dose CV monitoring; LFT/macular surveillance*
Tapinarof	**6.1**	Plaque psoriasis	**Topical**	*Topical cream — no meaningful systemic exposure regardless of LogP*
Moxidectin	**6.0**	Onchocerciasis	**Single-dose**	*Single-dose antiparasitic — total lifetime exposure is one dose*

Source: FDA CDER novel drug approvals 2016–2025 (calendar-year reports). LogP via PubChem XLogP3. Universe: oral small-molecule NMEs only; excludes biologics, peptides, oligonucleotides, reformulations, and combination products of approved actives; Scorpion Capital estimates and analysis

Obefazimod is one of the most lipophilic drugs ever developed

Obefazimod at LogP ~6 puts it squarely in the company of amiodarone, dronedarone, halofantrine, and bedaquiline -- drugs that are either (a) last-resort treatments for life-threatening conditions (TB, fatal arrhythmias), (b) withdrawn for safety, or (c) carry black box warnings. None of them are chronic-use GI drugs for a condition with numerous alternative drugs.

Obefazimod's lipophilicity profile is an extreme outlier, especially for a non-fatal indication

LogP ≥ 7

- **Amiodarone** — LogP ~7.6. The poster child for extreme lipophilicity in approved drugs. Massive tissue accumulation, half-life of 40–55 days, well-documented pulmonary fibrosis, thyroid toxicity, corneal deposits, hepatotoxicity, photosensitivity/blue-gray skin discoloration. A cautionary tale in pharmacology textbooks.
- **Dronedarone** — LogP ~7.1. Designed as a "safer amiodarone" by removing iodine and adding a methylsulfonamide group, but it remains a tertiary amine with high lipophilicity that is subject to ion trapping and may reproduce side effects caused by tissue deposits. Black box warning for heart failure mortality. Liver failure cases post-marketing.

LogP ~6–7

- **Halofantrine** — LogP ~6.5–7. Antimalarial. Withdrawn/restricted in most markets due to fatal QT prolongation and cardiotoxicity. Extreme tissue sequestration.
- **Lumefantrine** — LogP ~6.7. Antimalarial (used in the Coartem combination with artemether). Only viable because of the combination format and the acute-treatment context.
- **Bedaquiline** — cLogP ~6.4. TB drug. Analogs indicated a lower cLogP limit of about 5.0 in the series for retention of potent inhibitory activity against M.tb. nih Black box warning for increased mortality risk. QT prolongation. Extremely long half-life (~5.5 months) driven by tissue accumulation.
- **Ceritinib** — ALogP ~6.4. ALK inhibitor for NSCLC. Significant GI toxicity, hepatotoxicity, QT prolongation.

LogP ~5.5–6

- **Itraconazole** — LogP ~5.7. Antifungal. Negative inotropic effects (black box for CHF), hepatotoxicity.
- **Posaconazole** — LogP ~5.5. Antifungal. Similar class concerns.
- **Saquinavir** — LogP ~5.5. HIV protease inhibitor. QT prolongation warnings.
- **Tipranavir** — LogP ~6. HIV protease inhibitor. Black box for hepatotoxicity and intracranial hemorrhage.
- **Neratinib** — LogP ~5.7. HER2 inhibitor. Severe diarrhea.

Obefazimod's logP is extreme versus approved UC small molecules: only etrasimod is in the same vicinity -- its recent launch is a colossal failure; and it's micro-dosed at 2 mg/day vs. obefazimod's horse pill-like 25/50 mg.

FDA-approved oral small molecules for UC cluster at LogP of 1 to 3 with a few at ~4 – well within Lipinsksi's rule of 5. Only obefazimod and etrasimod (S1P modulator, 2023) are ~6 -- and etrasimod earned a baseline ECG, liver function tests for hepatotoxicity, baseline/ongoing ophthalmology monitoring, and extensive warnings for hypertension, fetal risk, pulmonary function, etc. Obefazimod has virtually no precedent in terms of dose × duration × lipophilicity in UC. Etrasimod is 2 mg/day. a low total daily dose for a high-affinity, membrane-localized target. Obefazimod 50 mg/day is ~25× higher mass exposure with an off-target binding profile.

LogP comparison -- approved UC small molecule drugs vs. obefazimod

Drug	Class	Approved	LogP	Safety / status
Obefazimod	*Candidate*	—	**~6.0**	**ANOMALY IN UC CLASS**
Etrasimod	*S1P modulator*	2023	**~6.0**	*Newest UC drug; CV monitoring*
Beclomethasone	*Corticosteroid*	ex-US	**4.6**	*Locally-acting; not US-approved*
Cyclosporine	*Calcineurin inh.*	off-label	**4.3**	*IV rescue only; off-label*
Ozanimod	*S1P modulator*	2021	**4.1**	*First-dose CV monitoring*
Tacrolimus	*Calcineurin inh.*	off-label	**2.7**	*Off-label severe UC; monitored*
Upadacitinib	*JAK1 inhibitor*	2022	**2.5**	*Black box: thrombosis/MACE*
Budesonide	*Locally-acting CS*	2013	**2.5**	*Approved (Uceris); local action*
Methylpred.	*Corticosteroid*	pre-1990	**1.8**	*Severe UC induction only*
Tofacitinib	*Pan-JAK inhibitor*	2018	**1.5**	*Approved competitor; black box*
Mesalamine	*5-Aminosalicylate*	pre-1990	**1.1**	*First-line UC; many formulations*
Sulfasalazine	*5-ASA prodrug*	pre-1990	**-0.4**	*Original 5-ASA; colonic release*

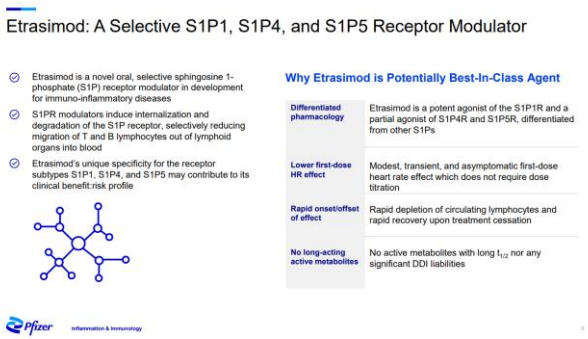
Source: PubChem (XLogP3), DrugBank, FDA labels. LogP values are PubChem XLogP3 (computed octanol/water partition). Approval years reflect FDA approval of the active moiety for UC..

Etrasimod's launch flop is the canary in the coal mine for obefazimod -- both lipophilic outliers. Pfizer paid $6.7B for Arena with $4B peak sales estimates – the asset already appears to be a total writeoff. Etrasimod's logP implies it's 100-1,000X more lipophilic than the leading S1P drug.

Pfizer acquired Arena Pharmaceuticals in 2021 for its etrasimod UC asset. The FDA approved it in Oct 2023 and it was launched as Velsipity. Pfizer quickly booked a $1.4B impairment charge in Jan 2024 -- suggesting the launch was dead-on-arrival – and appears to have quietly written off most of the remainder in Dec 2025, as the Feb 2026 earnings call indicated an additional $4.4B impairment. We see no mention of etrasimod in recent earnings calls or materials, suggesting sales are immaterial.

Timeline of Arena/Pfizer UC drug's (etrasimod) rapid failure and write-off

Dec 2021: Pfizer presentation talking up etrasimod as best-in-class



Etrasimod: A Selective S1P1, S1P4, and S1P5 Receptor Modulator

- Etrasimod is a novel oral, selective sphingosine 1-phosphate (S1P) receptor modulator in development for immuno-inflammatory diseases
- S1PR modulators induce internalization and degradation of the S1P receptor, selectively reducing migration of T and B lymphocytes out of lymphoid organs into blood
- Etrasimod's unique specificity for the receptor subtypes S1P1, S1P4, and S1P5 may contribute to its clinical benefit:risk profile

Why Etrasimod is Potentially Best-In-Class Agent

Differentiated pharmacology	Etrasimod is a potent agonist of the S1P1R and a partial agonist of S1P4R and S1P5R, differentiated from other S1Ps
Lower first-dose HR effect	Modest, transient, and asymptomatic first-dose heart rate effect which does not require dose titration
Rapid onset/offset of effect	Rapid depletion of circulating lymphocytes and rapid recovery upon treatment cessation
No long-acting active metabolites	No active metabolites with long $t_{1/2}$ nor any significant DDI liabilities

Pfizer Inflammation & Immunology

Oct 2023: FDA approval

FDA Approves Pfizer's Ulcerative Colitis Drug, $6.7B Arena Buy Pays Off

Jan 2024: First impairment charge

Pfizer Takes Impairment Charges On Velsipity And Prevnar 13

As we are increasingly focused on prioritizing our investments to drive forward-looking growth, our GAAP results include a $1.4 billion intangible asset impairment charge associated with etrasimod, based on a change in development plans for additional indications and overall revenue expectations, but I will point out

Feb 2026: Total write-off? PFE earnings call.

In support of our goal to enhance R&D productivity and focus on high-impact medicines, our fourth quarter GAAP results reflect strategic decisions in our development plans and **updated long-range revenue forecast for certain products** and pipeline assets. As a result, we recorded approximately **$4.4 billion of noncash intangible asset impairments** related to several medicines…

Source: https://s206.q4cdn.com/795948973/files/doc_presentation/2021/12/13/Final-II-Investor-Day-Triad_2-Presentation.pdf; https://s206.q4cdn.com/795948973/files/doc_financials/2023/q4/Q4-2023-Earnings-Conference-Call-Prepared-Remarks-FINAL.pdf; https://insights.citeline.com/SC149711/Pfizer-Takes-Impairment-Charges-On-Velsipity-And-Prevnar-13/

Chapter 8. Obefazimod's combination of properties – logP, TPSA, and others -- is unusual for a drug but resembles the signature of persistent organic pollutants (POPs) and certain agrochemicals.

A LogP 6 compound is a mass action drug, almost by definition -- at this level of lipophilicity, off-target membrane partitioning and intracellular accumulation overwhelm any purported selective upregulation of miR-124

Mass action means a drug's effects are driven by its physical accumulation in membranes rather than by selective binding to a specific molecular target. A selective drug binds one target at low concentrations. A mass action drug saturates membranes at concentrations high enough to alter their structure — disrupting membrane fluidity, interfering with membrane-bound proteins, and triggering downstream toxicity in tissues it reaches, regardless of what the drug was designed to do. At LogP 6, these membrane concentrations are guaranteed. Any mechanistic narrative about miR-124 is overwhelmed by the chemistry of a compound that partitions a million-to-one into lipid (octanol) over water.

Mass action compounds – extreme lipophilicity in this range is the defining characteristic of persistent organic pollutants

Compound	LogP	What happened	Status
 DDT	6.9	Bioaccumulates in adipose tissue, persists for decades, multi-generational toxicity	Banned globally (Stockholm Convention)
 TCDD (Dioxin)	6.8	Agent Orange contaminant, tissue half-life 7-11 years, multi-organ carcinogen	Banned / regulated as persistent organic pollutant
 PCBs	5-8	Still detectable in human tissue 40+ years after ban	Banned globally (Stockholm Convention)
 Hexachlorobenzene	5.7	Liver, thyroid, kidney toxicity; bioaccumulative	Banned globally
 **Obefazimod**	**~6**	**8 weeks of Phase 3 data; lipid/pancreatic signals emerging**	**To be dosed daily into humans**

Regulatory agencies view LogP >5 as a key screening threshold for bioaccumulation hazard

Obefazimod sits squarely in this range — and unlike these banned compounds, it would be dosed intentionally and chronically to patients with a non-fatal chronic disease.

Obefazimod displays environmental toxicant-grade lipophilicity similar to classic persistent organic pollutants (POP's), such as the infamous dirty dozen marked by the Stockholm Convention – DDT, dioxins, PCB's

Obefazimod's high lipophilicity puts it in the same logP neighborhood as classic persistent organic pollutants (POP's) such as pesticides and herbicides – DDT, dioxins, PCB's - whose biological behavior is dominated by lipid partitioning, tissue/organ retention, and slow clearance – accumulating in membranes, lipid droplets, liver, adipose tissue, blood cells, and other hydrophobic compartments. Environmental chemistry – and OECD bioaccumulation guidance - treats logP above 5 as a red-flag zone.

Obefazimod's logP is in the same hazard zone as the Stockholm Convention's 12 initial Persistent Organic Pollutants "causing adverse effects on humans and the ecosystem"

Stockholm Convention on Persistent Organic Pollutants (POPs)

The 12 initial POPs under the Stockholm Convention

Initially, twelve POPs have been recognized as causing adverse effects on humans and the ecosystem and these can be placed in 3 categories:

- **Pesticides**: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene;
- **Industrial chemicals**: hexachlorobenzene, polychlorinated biphenyls (PCBs); and
- **By-products**: hexachlorobenzene; polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), and PCBs.

Original Stockholm POPs: LogP / $\log K_{ow}$

Original Stockholm POP	Type	Representative logP / logKow
Aldrin	Pesticide	~6.5
Chlordane	Pesticide mixture	~6.0–6.2
DDT	Pesticide	~6.9
Dieldrin	Pesticide	~6.2
Endrin	Pesticide	~5.3–5.6
Heptachlor	Pesticide	~5.3
Hexachlorobenzene	Pesticide / industrial byproduct	~5.7–6.2
Mirex	Pesticide / flame retardant	~5.3
Toxaphene	Pesticide mixture	~5.9 median; range ~3.3–6.6
PCBs	Industrial chemicals	~4.7–8.2
Dioxins / PCDDs	Industrial byproducts	~6.5–7.7
Furans / PCDFs	Industrial byproducts	~6.5–7.0+

Source: https://chm.pops.int/theconvention/thepops/the12initialpops/tabid/296/default.aspx

High lipophilicity is a core feature of pesticides, enabling penetration of membranes which are lipid layers. The agricultural chemistry literature indicates an obefazimod-like logP ~6 is hazardous even for a pesticide.

Elevated lipophilicity/hydrophobicity, measured by logP, is a defining feature of insecticides and herbicides as it promotes membrane partitioning, penetration, transport, and target-site activity. However, the pesticide literature indicates an optimal window, since excessive lipophilicity leads to high persistence in membranes, driving bioaccumulation and toxicity in the food chain and environment. The papers indicate that logP > ~3 is therefore undesirable for pesticides – which makes obefazimod (logP of ~6) 1000X more lipophilic than this ceiling and 10X more than many others.

Pesticides are highly lipophilic but logP > ~3 is excessive even by pesticide standards, tending to "bind to hydrophobic targets, increasing risk of nonselectivity and toxicity" - obefazimod's logP ~6 1,000X more lipophilic.

LIPOPHILIC PROPERTIES OF PESTICIDES: BIOACCUMULATION AND BIOMAGNIFICATION IN ANIMALS, THE TOXICITY FORECASTING
(review)

Organochlorine pesticides are highly lipophilic, persistent, toxic, and bio-accumulative [42]. The most dangerous are 4,4-dichlorodiphenyl trichloromethyl-methane (DDT) and γ-hexachlorocyclohexane (γ-HCH, lindane), logP 6.91 and 3.72, respectively [43]. They can persist in soils for many years, are resistant to degradation, have estrogenic and carcinogenic properties, and are banned for use in most countries [2, 44]. Organophosphate pesticides, carbamates and pyrethroids are now more widely used due to their lower persistence than in organochlorines.

easier passage of the blood-brain barrier. Too high a lipophilicity (logP > 2.8), on the contrary, can lead to increased nonspecific binding to plasma proteins (36). Compounds that are excessively lipophilic (logP > 5) tend to bind to hydrophobic targets, increasing the risk of nonselectivity and toxicity [39].

Importance of Physicochemical Properties for the Design of New Pesticides

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ABSTRACT: The physicochemical properties of candidate compounds play important roles in the design of new pesticides. Pesticides must be absorbed by pests, be transported to the target site, and then interact with proteins. Hydrophobicity is very important for these processes. Log *P*, where *P* is the partition coefficient in the 1-octanol/water system, is commonly used as a hydrophobic descriptor and correlates with membrane permeation and transport. It was recently reported that permeability by the parallel artificial membrane permeation assay (PAMPA) could be used to predict human oral absorption of passively transported compounds. PAMPA, which is a rapid high-throughput screening system, may be useful to predict pesticide absorption because PAMPA permeability can be calculated using log *P* and other parameters. Electronic and structural properties as well as hydrophobicity are important factors for protein−ligand interaction. To show the importance of physicochemical properties, the classic QSAR and CoMFA of neonicotinoids and prediction of bioavailability of pesticides in terms of membrane permeability in comparison with drugs are described.

"The physicochemical properties of candidate compounds play important roles in the design of new pesticides. Pesticides must be absorbed by pests, be transported to the target site, and then interact with proteins. Hydrophobicity is very important for these processes. Log P, where P is the partition coefficient in the 1-octanol/water system, is commonly used as a hydrophobic descriptor and correlates with membrane permeation and transport."

Source: https://www.agrobiology.ru/articles/6-2023kish-eng.pdf; https://pubmed.ncbi.nlm.nih.gov/20879794/

Obefazimod's LogP is higher than almost every mainstream pesticide and herbicide shown in a study. Only 2 of 45 sit in a similar danger zone – their lipophilicity drives neurotoxicity by penetrating lipid-rich nerve membranes.

A pesticide-design study on lipophilic-driven membrane penetration lists 25 mainstream pesticides and 20 herbicides. Obefazimod logP of ~6 is an outlier exceeding all but 2 of 25 pesticides – and exceeds all 20 herbicides. Of the two pesticides, one has similar logP and the other is only log unit higher. The logP of the most lipophilic herbicide is 5.07 – which makes obefazimod 10X more lipophilic. That herbicide – trifuralin – is banned in the EU due to its potential for bioaccumulation and toxicity, and reguled in the US as a Hazardous Air Pollutant. The two pesticides - etofenprox and tefluthrin – are on regulatory watchlists and received flimsy renewals due to reglued lipophilicity, bioaccumulation risk, and toxicity.

Obefazimod lipophilicity is extreme even vs. insecticides/herbicides

Importance of physicochemical properties for the design of new pesticides

Insecticides

compd no.	compd name	log $P_{app\text{-}PAMPA}$ (measured)	log P
	insecticides		
1	imidacloprid	−5.34	0.59
2	RH-5849	−4.78	2.45
3	DMTP	−4.97	2.50
4	salithion	−5.03	2.67
5	chromafenozide	−4.78	2.70
6	BPMC	−4.91	2.78
7	halofenozide	−4.76	3.22
8	fenitrothion	−5.55	3.30
9	diazinon	−5.28	3.30
10	phenthoate	−6.24	3.96
11	methoxyfenozide	−4.72	3.70
12	fenthion	−6.14	4.09
13	tebufenozide	−4.80	4.25
14	acephate		−0.85
15	acetamiprid		
16	etoxazole		
17	etofenprox		7.05
18	chlorfenapyr		4.83
19	dinotefuran		-
20	tefluthrin		6.00
21	fipronil		4.00
22	benfuracarb		4.30
23	fosthiazate		
24	methomyl		0.60
25	clothianidin		

Herbicides

compd no.	compd name	log $P_{app\text{-}PAMPA}$ (measured)	log P
	herbicides		
1	atrazine	−4.53	2.61
2	benthiocarb	−4.69	3.42
3	butamifos	−6.40	4.62
4	2,4-D		2.81
5	bensulfuron-methyl		
6	dichlobenil		2.74
7	diuron		2.68
8	linuron		3.20
9	bentazone		2.80
10	bromacil		2.11
11	sethoxydim		-
12	trifluralin		5.07
13	cyanazin		2.22
14	oxaziclomefone		
15	dymron		
16	esprocarb		4.60
17	asulam		−0.27
18	isouron		1.98
19	alachlor		3.52
20	karbutilate		1.66

Agrochemicals with lipophilicity similar to obefazimod

- **Trifluralin –** organofluroine herbicide banned in EU due to "high" potential for bioaccumulation and environmental toxicity; EPA-regulated as a Hazardous Air Pollutant
- **Etofenprox** and tefluthrin – highly lipophilic (logP 7 and 6) insecticides that penetrate lipid-rich nerve membranes

Mechanisms of Toxic Action and Structure-Activity Relationships for Organochlorine and Synthetic Pyrethroid Insecticides

"Lipophilicity is important for all the groups because it facilitates delivery of these neurotoxicants to the site of action in the nerve."

Source: https://pubmed.ncbi.nlm.nih.gov/20879794/; https://www.researchgate.net/publication/20978645_Mechanisms_of_toxic_action_and_structure-activity_relationships_for_organochlorine_and_synthetic_pyrethroid_insecticides

Obefazimod's molecular fingerprint shares key similarities with classic agrochemicals such as pesticides and persistent organic pollutants

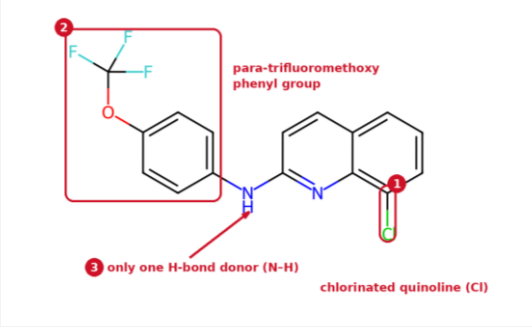
Obefazimod combines the structural features that drive POP/agrochemical behavior -- halogenation, heavy aromaticity, LogP ~6 -- on a small-molecule scaffold for chronic oral use.

Obefazimod shares several chemical features that made organohalogen pesticides and POP's problematic - high lipophilicity, halogenation, aromatic

1. Small halogenated aromatic molecule exhibiting the basic pesticide/ POP-like chemical fingerprint

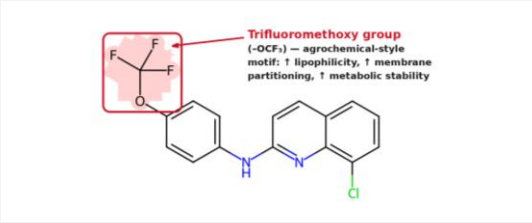
Obefazimod is 8-chloro-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine, formula **C16H10ClF3N2O, with:**

- a **chlorinated quinoline** ring system;
- a **para-trifluoromethoxy phenyl** group;
- only one **H-bond donor**



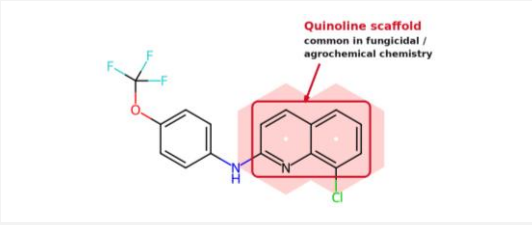
2. Trifluoromethoxy group is an agrochemical-style characteristic

The trifluoromethoxy group makes a molecule more lipophilic, increases membrane-partitioning, and makes it harder to metabolically chew up.



3. Quinoline scaffolds are common in fungicidal/agrochemical chemistry

Quinoline derivatives/scaffolds are used in pesticides/fungicides. Quinoxyfen, for example, is a commercial fungicide with a halogenated quinoline/quinoline-like aryl ether structure used against powdery mildew. More broadly, quinoline compounds exhibit antifungal, herbicidal, and anti-insecticidal activity.

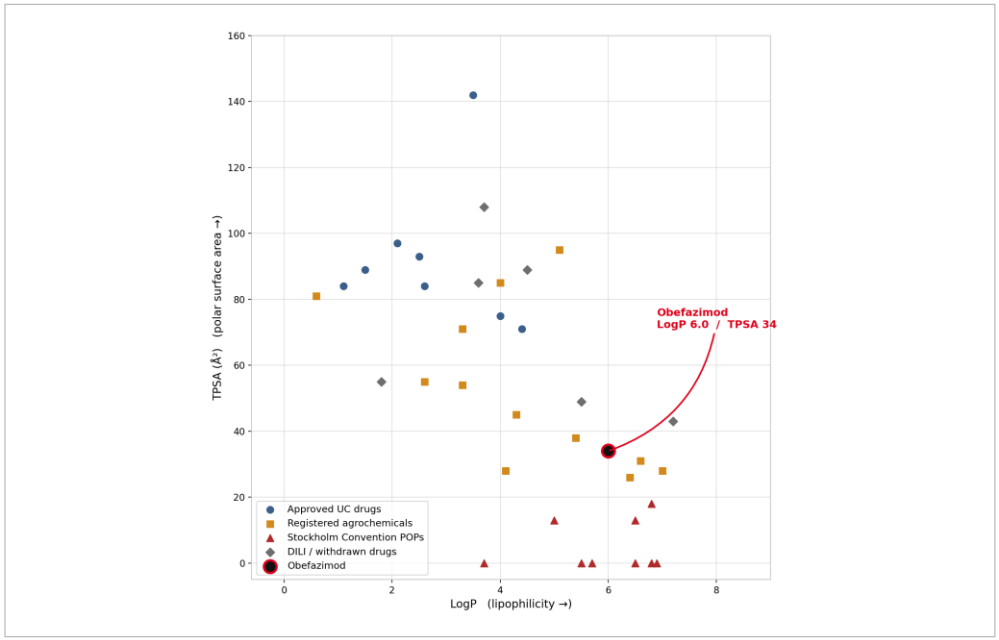


Sources: National Center for Biotechnology Information (PubChem CID 78241411 for Obefazimod structural data; CID 3391107 for Quinoxyfen agrochemical usage); Literature consensus on the -OCF3 motif driving lipophilicity and enzymatic degradation resistance. For 1), specifically: PubChem Compound Summary for CID 78241411; 2) general medicinal and agrochemical chemistry literature on fluorinated ethers; 3) PubChem Compound Summary for CID 3391107 (Quinoxyfen) and the University of California Statewide Integrated Pest Management Program (UC IPM)

Obefazimod's LogP + TPSA combination is unusual for a drug – but is the same signature as agrochemicals and Stockholm Convention persistent organic pollutants.

Obefazimod pairs agrochemical-range lipophilicity (LogP ~6) with a polar surface area of 34 Å² — low even by agrochemical standards. High LogP and low TPSA together describe a molecule that crosses membranes freely and partitions into fat, with little of the polarity that drives renal or biliary clearance – a similar profile to DDT, dieldrin and chlordane, and of amiodarone, the one approved drug on the chart with the same combination. Not one approved UC therapy comes close. Stockholm Convention POPs were organ halogen banned not for acute toxicity but because they accumulated in tissue and caused harm that short-term studies could not capture. Obefazimod carries the same physicochemical signature, which predicts the program's PK/dosing struggles and chronic-exposure liability.

TPSA vs. LogP - obefazimod sits in the bottom right quadrant next to agrochemicals/POP's



Compound	LogP	TPSA
OBEFAZIMOD		
Obefazimod	**6.0**	**34**
APPROVED UC ORAL DRUGS		
tofacitinib	1.5	89
upadacitinib	2.6	84
filgotinib	2.1	97
etrasimod	4.0	75
ozanimod	4.4	71
mesalamine	1.1	84
budesonide	2.5	93
sulfasalazine	3.5	142
DILI / WITHDRAWN PRECEDENTS		
amiodarone	7.2	43
dronedarone	4.5	89
troglitazone	3.6	85
lumiracoxib	5.5	49
sitaxentan	3.7	108
pemoline	1.8	55

Compound	LogP	TPSA
REGISTERED AGROCHEMICALS		
tefluthrin	6.4	26
etofenprox	7.0	28
fipronil	4.0	85
fenitrothion	3.3	71
diazinon	3.3	54
fenthion	4.1	28
tebufenozide	4.3	45
atrazine	2.6	55
trifluralin	5.1	95
chlorfenapyr	5.4	38
etoxazole	6.6	31
imidacloprid	0.6	81

Compound	LogP	TPSA
STOCKHOLM CONVENTION POPs		
DDT	6.9	0
dieldrin	6.5	13
aldrin	5.5	0
endrin	5.0	13
lindane	3.7	0
hexachlorobenzene	5.7	0
PCB-153	6.5	0
chlordane	6.8	0
2,3,7,8-TCDD	6.8	18

Sources: LogP (lipophilicity) — Akamatsu, *J. Agric. Food Chem.* 2011, Table 2 (agrochemicals); experimental/XLogP3 values from DrugBank and PubChem (drugs); PubChem (POPs). TPSA — topological polar surface area computed by the Ertl et al. (2000) fragment method over polar N and O atoms, applied uniformly to all compounds (RDKit, 2024). Obefazimod: LogP ~6.0 (literature range 5.9–6.2); TPSA 34 Å² (PubChem CID 49846599, https://pubchem.ncbi.nlm.nih.gov/compound/49846599). Stockholm Convention POPs listed under Annexes A/B/C.

Obefazimod's LogP + TPSA combination is in a similar zone to some of the most notable post-approval withdrawals for DILI - drug-induced liver injury

The drugs below were approved on short-term trial data but accumulated a post-approval safety signal predicted by the molecular profile - withdrawal or black-box warning within 2–4 years in non-life-threatening indications. Amiodarone is the exception, staying on market only because the alternative is sudden cardiac death - unlike ulcerative colitis which is not fatal.

Historical pattern for compounds with this LogP/TPSA profile in non-life-threatening indications: withdrawal or black-box warning within a few years of chronic exposure

Drug	Class / Indication	LogP	TPSA	Indication risk	Approved	Regulatory outcome	Mechanism
Amiodarone	Antiarrhythmic	7.2	43	*Life-threatening*	1985	**BBW** from launch; tolerated due to indication	Phospholipidosis, mitochondrial dysfunction, tissue accumulation
Dronedarone	Antiarrhythmic	4.5	83	Non-life-threatening	2009	**2× BBW** within 2 years (heart failure, hepatotoxicity)	Mitochondrial dysfunction, hepatotoxicity
Troglitazone	Antidiabetic (T2D)	3.6	93	Non-life-threatening	1997	**Withdrawn** 2000 (3 years)	Reactive quinone methide, BSEP inhibition, mitochondrial
Lumiracoxib	COX-2 / pain	5.5	49	Non-life-threatening	2003 (EU)	**Withdrawn** 2007–08 (4 years)	Reactive metabolite from halogenated aromatic; never US-approved
Sitaxentan	Endothelin / PAH	3.7	99	*Serious but treatable*	2006 (EU)	**Withdrawn** 2010 (4 years)	Idiosyncratic hepatotoxicity from scaffold-specific reactive metabolite
Pemoline	CNS stimulant / ADHD	1.8	55	Non-life-threatening	1975	**Withdrawn** 2005 (30 years; tipped when alternatives emerged)	Acute hepatic failure (13× population rate)
Obefazimod	**Anti-inflammatory / UC**	**~6.0**	**~34**	**Non-life-threatening**	**???**	**???**	**???**

Sources: FDA Orange Book and label histories; LiverTox (NIH NLM); DrugBank/PubChem for physicochemical properties; Watkins (2005) on troglitazone; published DILI case series.
Excludes successful high-LogP chronic-dose drugs (statins, azoles, kinase inhibitors) where structural mitigants or indication risk justify approval.

Mass action drugs are unsurprisingly one of the most troubled and toxic class of therapeutics: they tend to require a life-threatening indication and/or end up being pulled from the market

Banned pollutants are among the most well-known mass action compounds. However, the pharmaceutical industry has its own history with mass action. Every drug with physicochemistry in this lipophilicity range has produced multi-organ toxicity driven by membrane accumulation. The pattern is consistent: the higher the LogP, the broader the toxicity; and the narrower and more fatal the indication it's intended for. We are not aware of any mass action drug has ever been approved for a chronic non-fatal condition like UC when multiple safer alternatives are available.

Mass action drugs tend to treat conditions that are fatal without intervention -- and/or were withdrawn

LogP **3.6**	**Chloroquine / HCQ** Irreversible retinal maculopathy (7-8% after 5+ yrs), cardiomyopathy. Lysosomal accumulation drives toxicity.	**TOLERATED** — lupus/malaria Mandatory eye monitoring for life
LogP **~5.5**	**Terfenadine** Fatal cardiac arrhythmias via hERG channel blockade. An antihistamine — mass action killed patients taking it for hay fever.	**WITHDRAWN 1998** Replaced by fexofenadine
LogP **~6**	**Dronedarone** Designed as "safer amiodarone." Still caused increased mortality in the PALLAS trial. Hepatotoxicity, cardiovascular death.	**BLACK-BOXED** Severely restricted
LogP **7.6**	**Amiodarone** Pulmonary fibrosis (fatal 1-5%), thyroid destruction (15-20%), corneal deposits, hepatotoxicity, peripheral neuropathy, blue-gray skin.	**TOLERATED** — lethal arrhythmias only Multi-organ monitoring for life
LogP **~6**	**Obefazimod** 8 weeks of Phase 3 data. Lipid/pancreatic cluster already emerging. No published tissue PK we could locate.	**BEING DEVELOPED FOR UC** Non-fatal, 5+ approved alternatives

Mass action chemistry is acceptable only when the disease is severe enough to warrant the trade-off and inevitable toll -- UC obviously does not

The tolerability bar depends on both reversibility and clinical need. Mass action drugs like volatile anesthetics are fully reversible and wash out in minutes. Amiodarone can persist for months and injure multiple organs, but life-threatening arrhythmias justify that burden. Hydroxychloroquine is accepted in lupus with lifelong retinal monitoring. Terfenadine's cardiac risk was not acceptable for hay fever, and the drug was withdrawn. Obefazimod pairs Tier 3–4 physicochemistry with a Tier 1 indication—ulcerative colitis, where several approved alternatives already exist. The risk-benefit fit is implausible.

Mass action tolerability spectrum: obefazimod has the toxicity profile of Tier 3-4 drugs – last resort or pulled/restricted -- but the indication of a Tier 1

TIER 1 — TOLERABLE — Brief or low-dose exposure. Mass action is controlled or subclinical.	
Volatile anesthetics	Wash in/out in minutes. Mass action IS the mechanism. Fully reversible.
Azithromycin	5-day courses. Lysosomal concentration is therapeutic. Billions of prescriptions.
SSRIs (fluoxetine)	Phospholipidosis inducer in vitro, subclinical at therapeutic doses.
TIER 2 — MONITOR CLOSELY — Known toxicity, managed with lifelong surveillance. Justified for serious disease.	
Hydroxychloroquine	t½ 40-50d. Irreversible retinal damage ~7-8% after 5+ yrs. Annual eye exams. Justified for lupus.
Chloroquine	More toxic than HCQ. Higher retinopathy. Replaced by HCQ for chronic use.
TIER 3 — LAST RESORT — Severe multi-organ toxicity. Tolerated only because the alternative is death.	
Amiodarone (LogP 7.6)	Pulmonary, hepatic, thyroid, corneal, neural toxicity. Multi-organ monitoring for life. Lethal arrhythmias only.
Amphotericin B	"Ampho-terrible." Nephrotoxicity near universal. Tolerated for fatal fungal infections only.
TIER 4 — PULLED / RESTRICTED — Too toxic even when it works. Withdrawn or black-boxed.	
Dronedarone (~LogP 6)	"Safer amiodarone" — still caused increased mortality (PALLAS trial). Black-boxed.
Terfenadine (~LogP 5.5)	Antihistamine causing fatal arrhythmias. Withdrawn 1998.
Ketoconazole (oral)	Severe hepatotoxicity. Withdrawn for systemic use 2013. Safer alternatives existed.

OBEFAZIMOD (LogP ~6) Tier 3-4 physicochemistry being developed for a Tier 1 indication. UC is non-fatal, has multiple approved alternatives.

Obefazimod lacks the safeguards that make other mass-action drugs tolerable

Brief exposure, reversibility, restricted distribution, intensive monitoring, or a life-threatening indication can justify mass-action pharmacology. Obefazimod has none of those protections: it is a neutral, highly lipophilic drug intended for chronic daily use in a non-fatal disease with multiple approved alternatives.

The acceptable justifications to accept and risk mass-action toxicity do not apply to obefazimod

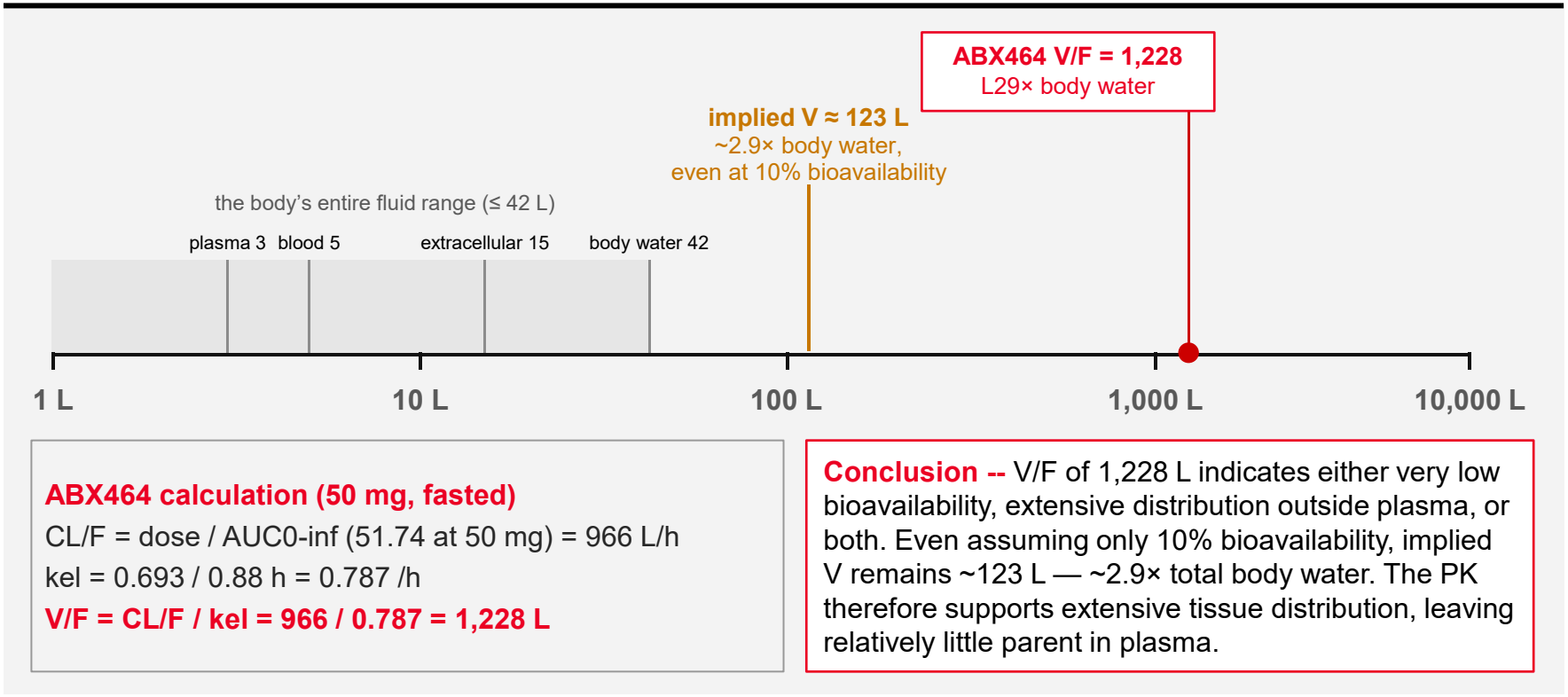
Safeguard	Accepted mass-action drugs	Obefazimod
Exposure is brief or reversible	Volatile anesthetics, azithromycin	Chronic daily dosing; long terminal half-life and accumulation
Disease is life-threatening	Amiodarone, amphotericin B	Ulcerative colitis is serious but non-fatal; several approved alternatives
Toxicity is actively monitored	Hydroxychloroquine, amiodarone	No tissue-burden monitoring or analogous surveillance
Distribution is constrained or targeted	Topical, gut-restricted, or organ-localized drugs	Neutral, high-logP molecule expected to distribute broadly into lipids
Adequate alternatives are limited	Fatal arrhythmia, invasive fungal infection	Five or more approved alternatives already exist

Bottom line: obefazimod combines high-risk mass-action chemistry with a disease setting that offers no comparable justification

Chapter 9. Obefazimod's own PK data undermine its purported "short half-life" story.

ABX464's calculated V/F is 1,228 L – ~29x-44x total body water; even at 10% bioavailability, implied V is ~123L, consistent with extensive distribution out of plasma and into tissue.

ABVX's published PK data (Scherrer 2017) provide the inputs but not the V/F value; we calculate V/F of 1,228 L — ~29×-~44x total body water, depending on which Scherrer study ones uses for the calculation. Because oral V/F is inflated by incomplete bioavailability, even assuming only 10% bioavailability implies V of ~123 L — still ~2.9× total body water. Vd is not a physical volume: it measures how little drug remains in plasma relative to the amount in the body. A value this large is consistent with extensive distribution outside plasma and into tissue.



ABX464 calculation (50 mg, fasted)

CL/F = dose / AUC0-inf (51.74 at 50 mg) = 966 L/h

kel = 0.693 / 0.88 h = 0.787 /h

V/F = CL/F / kel = 966 / 0.787 = 1,228 L

Conclusion -- V/F of 1,228 L indicates either very low bioavailability, extensive distribution outside plasma, or both. Even assuming only 10% bioavailability, implied V remains ~123 L — ~2.9× total body water. The PK therefore supports extensive tissue distribution, leaving relatively little parent in plasma.

Sources: https://doi.org/10.1128/AAC.01288-16; *Scherrer 2017, Antimicrob Agents Chemother 61(1):e01288-16 (food study, Table S1)*. Reference volumes: standard human physiology (70 kg); Scorpion Capital estimates and analysis.

ABVX reports plasma PK without disclosing the blood-to-plasma ratio or protein binding needed to interpret it – including how much parent may be sequestered in red blood cells. RBC partitioning could make plasma PK dramatically understate tissue exposure.

ABX464 is a neutral logP ~6 lipophile expected to partition into RBC membranes and plasma proteins/lipoproteins. Without blood-to-plasma partitioning and protein-binding data, plasma PK cannot establish total circulating parent exposure or reliably interpret tissue distribution -- and may materially understate parent exposure..

RED BLOOD CELL PARTITIONING

- A neutral drug at logP 6.35 dissolves into lipid bilayers, including red cell membranes. For many drugs of this class, the RBC pool accounts for 90% or more of circulating drug
- Red cells are 45% of blood volume. Drug held in their membranes will be discarded when plasma is separated for assay
- If RBC partitioning is substantial, plasma concentration can materially underestimate whole-blood parent exposure and distort plasma-derived PK parameters
- Our literature search could locate no blood fractionation studies disclosed by Abivax.

PLASMA PROTEIN BINDING

- Neutral logP 6.35 compounds are generally highly associated with lipoproteins. Benzo[a]pyrene (logP 6.13) is 93% lipoprotein associated.
- Only unbound drug is filtered by the kidney, metabolized by the liver or available to targets.
- Our search found no protein binding metrics, but neutral N-glucuronides are poorly protein bound as a class (Järvinen 2022).
- Our literature search could find no plasma protein binding studies disclosed by Abivax.

WHY THE MISSING DATA MATTER:

- **Clearance.** Blood clearance parameters require the blood-to-plasma ratio. Hepatic and renal clearance of parent depend on the unbound fraction of drug.
- **Distribution.** V/F reflects binding in plasma against binding in tissue. Without both values it cannot be divided between red cell, plasma protein and tissue pools.
- **Tissue uptake.** Lipoprotein-associated drug would enter cells through lipoprotein receptors. Red cells may act as a circulating reservoir for drug (covered in later slides).

ABX464's published PK is plasma-only: without B/P and protein-binding data, plasma concentrations cannot be reconciled to whole-blood parent exposure or tissue distribution

Sources: ICH M3(R2); FDA renal impairment PK guidance 2024; Biagiotti 2023; Scherrer 2017; Steens 2017; US 2024/0182422

Neutral high-logP compounds load into tissue and persist -- ABX464 sits directly in this class and exhibits the profile of a potent tissue accumulator. Plasma does not predict tissue levels for this class of drugs.

These comparators are neutral and un-ionized, so they accumulate by lipid partitioning, not by the lysosomal ion-trapping of cationic drugs (amiodarone, chloroquine). Benzo[a]pyrene and dioxin are also AhR agonists.

Neutral Compound	log P	Vd	Neutral	Tissue distribution published	Persistence in humans
Benzo[a]pyrene	6.1	78,019 human	Yes	Concentrates highly in tissues	22 days
TCDD (dioxin)	6.8	NC	Yes	Concentrates highly in tissues	~7 years
PCB-153	6.9	NC	Yes	Concentrates highly in tissues	~14 years
DDT	6.5-6.9	NC	Yes	Huge adipose:blood ratios, 280:1 in human and ~400:1 in rat	decades
ABX464	**6.35**	**1228 human**	**Yes**	**Predicted to load tissues (high Vd), We found no biodistribution or mass balance studies to confirm.**	**Our modeling estimates months in humans**

NC = not calculated

THE PRINCIPLE. For neutral drugs, the tissue-to-plasma ratio and the volume of distribution scales with log P and the lipid content of each tissue (Poulin & Theil 2000; Rodgers & Rowland 2006). ABX464 carries no charge, according to the findings from our research and analysis. Its log P of 6.35 places it in the same class as the neutral lipid-partitioning toxicants above. All load tissues and clear slowly.

Sources: Poulin & Theil 2000; Rodgers & Rowland 2006; Pirkle et al. 1989; Ritter et al. 2011; ATSDR Toxicological Profile for DDT, DDE, DDD; ATSDR Toxicological Profile for PAHs; Madeen et al. 2019

ABVX has not published the complete repeat-dose PK needed to explain where ABX464 goes under chronic dosing. Our review leads us to conclude that the "missing" plasma exposure is redistributing into tissue, not leaving the body.

Across the public PK studies we found, none provides complete QD repeat-dose concentration-time curves and terminal half-lives for both parent and N-Glu. The most striking repeat-dose result -- N-Glu AUC ~17× lower and Cmax ~5× lower in ART-treated patients -- was reported without the underlying curves, tables or a mechanistic explanation..

Study	Population	Co-administered therapies	Regimen	PK / observation
Scherrer 2017a	Healthy (n=24)	None	4 doses once every 3 days	Q3D, tables only
Scherrer 2017b	Healthy (n=24)	None	Single dose, dose-escalation: 50, 100, 150 or 200 mg)	Single dose, tables only
Steens 2017	Treatment-naive HIV+	None	50 mg QD or TID × 14 to 21 days	Repeated QD doses, tables only Parameters for the last dose are omitted
Rutsaert S 2019	ART - HIV+	*protease inhibitors (darunavir/ritonavir or darunavir/cobicistat)*	50 & 150 QD × 28 days	No tables or figures. Discussion: **N-Glu AUC 17x lower in ART patients – no explanation**
NCT02990325 Cohort 1	HIV+	integrase inhibitor (DTG or RAL) + NRTI (TDF/FTC or ABC/3TC)	150 mg QD × 28 days	**Only AUC & Cmax, no t1/2** **Parent ↓ 52% by D28** **N-Glu ≤1.3-fold accumulation**
NCT02990325 Cohort 3	HIV+	integrase inhibitor (DTG or RAL) + NRTI (TDF/FTC or ABC/3TC)	50 mg QD × 84 days	**Only AUC & Cmax,** **Parent ↓ 47% by D28 and D84;** **N-Glu ≤1.3-fold accumulation**

The only repeat-dosing N-Glu data show only AUC & Cmax with no time concentration curves or complete PK datasets that include both exposures, Tmax and half-life (no clearance or half-life). The only information we could find about N-Glu with repeated dosing was that given by Rutsaert, "after ABX464 repeated administration in participants receiving combined therapy as compared to previous results in untreated HIV-1-positive individuals."

Abivax did not disclose the half-life in any repeat dosing PK. Accumulation was 3-5-fold lower than predicted in our modeling studies. If the half-life is unchanged (it was not given) then the drug is being sequestered in tissue.

Rutsaert 2019 reports the Cmax and AUC of N-Glu was roughly 5x and 17x lower following treatment with protease inhibitors that block enterohepatic recirculation (EHR). Blocking EHR would blunt the 2nd peak, decreasing the AUC more than Cmax.

Sources: Scherrer et al. 2017a; Scherrer et al. 2017b; Steens et al. 2017; Rutsaert et al. 2019; NCT02990325, Cohorts 1 and 3

ABVX's PK data is sparse with glaring omissions and inconsistencies – key measurements needed to understand drug persistence, tissue distribution, and elimination are missing, including basic parameters the FDA requires.

1 Enterohepatic recirculation (EHR)
N-Glu is likely deconjugated by gut bacteria and reabsorbed, creating a recycling loop that extends effective half-life and tissue loading. Abivax has not discussed this publicly in any publication or investor materials we could find.

2 Time limited PK of parent
Plasma levels fall mainly because drug distributes into tissue, not because it is cleared from the body.

3 N-Glu, species limitation
Primates and mice form N-Glu at small fractions compared with humans, so preclinical exposure is unlikely to establish a valid safety margin. The protocol summaries are vague on exposure coverage.

4 Unmodeled terminal PK
Reported single-dose half-lives are ~0.7–1.6 h for parent and ~3.6–4.2 days for N-Glu. Our reanalysis identifies additional kinetic components in the published curves that were not separately modeled or reported; repeat-dose studies provide no terminal half-life or complete concentration-time curves.

5 Biodistribution and mass balance
We found no QWBA (quantitative whole-body autoradiography) or mass balance disclosure for a drug with a volume of distribution ~29 times total body water, dosed once daily. Four doses are taken before the first clears by half.

6 Plasma protein binding (PPB)
Standard ADME requirement per ICH M3(R2), not disclosed despite logP ~ 6 predicting poor aqueous solubility.

7 Red blood cell partitioning
Not disclosed. With logP >6 and neutral character, partitioning into the red cell membrane is expected and would mask true drug exposure. 15-20-fold ratios of blood to plasma ratios are not uncommon amongst or comparator compounds.

8 pKa (acid dissociation constant) not disclosed
We commissioned a CRO to measure pKa. The pKa was below 2, so ABX464 is neutral at physiological and lysosomal pH. It would therefore distribute into membranes and organelles with no charged component to limit uptake.

9 Key routes of elimination not disclosed
Abivax has published no mass balance we could find, so the split between biliary, renal and fecal elimination is unknown. Abivax see no published mass spectrometry imaging (MSI), LC-MS/MS tissue distribution, or accelerator mass spectrometry (AMS) studies to assess tissue distribution – for a logP 6.35 drug, that is a concerning omission.

10 Preclinical EHR studies not disclosed
The standard tests include bile duct cannulated rat; the linked rat bile transfer study; dosing in antibiotic treated animals; a cholestyramine challenge; incubation of drug with caecal contents; and MRP2 and BCRP substrate assays. None appear in the public record we reviewed. We note that drugs that are substrates for 3 of the EHR transporters, UGT9, OATP1B1 and OATP1B2 are prohibited in the Clinical Protocol 104.

Sources: Roberts & Magnusson 2002; Yanez et al. 2011; Chiu & Huskey 1998; ICH M3(R2) 2009; NCBI Bookshelf NBK545280; McEwen & Henson 2015; Vater et al. 2017; de Duve et al. 1974

Abivax reports a ~1-hour parent half-life but does not publish the complete QD repeat-dose PK needed to show whether that half-life holds under chronic dosing.

Published studies provide single-dose and Q72H parent parameters, but no complete QD repeat-dose concentration-time curves, clearance or terminal half-life. The available parent parameters already fail a simple first-order consistency check; the next slide shows the same anomalous post-peak behavior across all four published dose curves.

Abivax reported a terminal half-life of 0.74 to 1.15 hours for the parent. Food increased parent exposure ~3.7-fold. We could find no curves or tables for QD repeated-dose studies except for the ClinTrials.gov NCT02990325 post we discuss later, and that post only comprised AUC, Cmax and Tmax on days 1, 28 and 84 (no half-lives or clearance).

Published PK parameters for parent ABX464 and N-Glu at 50 mg, fasted and fed, across studies, Scherrer 2017b

Study and arm	State	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng·h/mL)	AUC0-∞ (ng·h/mL)	t1/2 (h)	n
Scherrer et al. 2017b, single dose	Fasted	14	1.75	41	42	1.09	6
Scherrer et al. 2017a, group 1, single dose	Fasted	18	1.5	43	52	0.88	23 / 17
Scherrer et al. 2017a, group 2, day 1	Fasted	11	1.75	31	not reported	1.11	12 / 4
Scherrer et al. 2017a, group 2, day 10	Fasted	11	1.8	28	not reported	1.15	12 / 9
Scherrer et al. 2017a, group 1, single dose	Fed	50	2.8	122	136	0.87	24 / 13
Scherrer et al. 2017a, group 2, day 1	Fed	47	2.50	113	not reported	0.77	12 / 6
Scherrer et al. 2017a, group 2, day 10	Fed	55	2.3	111	not reported	0.74	12 / 8

The published n and mean value for each pharmacokinetic parameter provided by Scherrer 2017a and b.

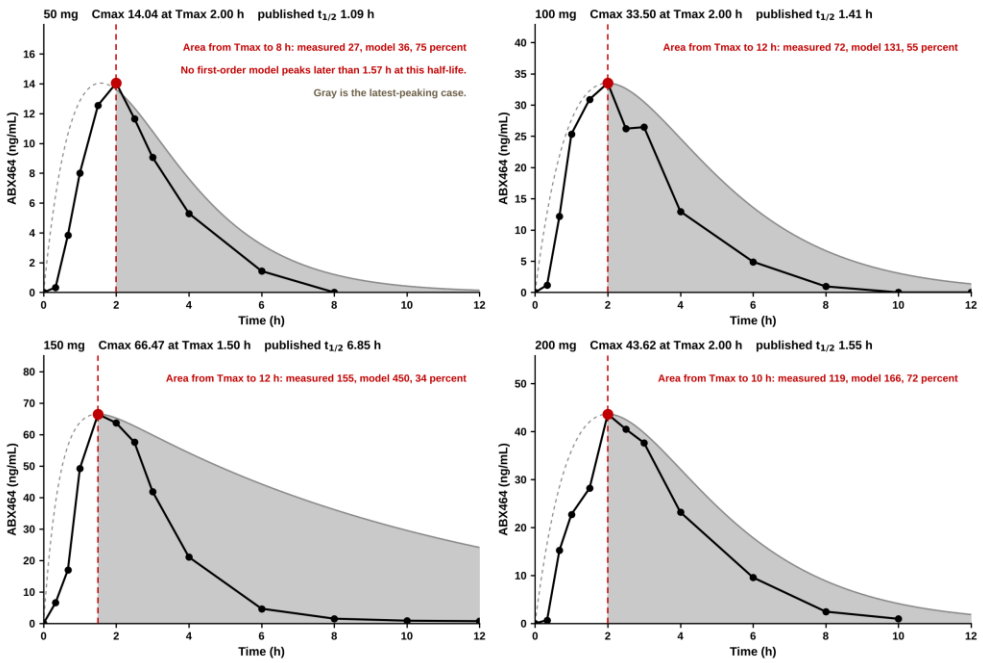
For parent, the median Cmax exceeded 1.44 times the reported terminal half-life in most of the published parameter sets (Scherrer 2017b, Table 3; Scherrer 2017a, Tables 1 and 3) suggesting that it does not conform to first order elimination kinetics.

Sources: Scherrer 2017a, Antimicrob Agents Chemother 2017;61(1):e01288-16; Scherrer 2017b, J Antimicrob Chemother 2017;72(3):820-828; Roanes-Lozano et al. 2006;

All four ABX464 parent PK curves show the same anomaly: parent vanishes from plasma faster than first-order elimination predicts -- consistent with rapid redistribution into tissue

Across 50–200 mg, the published parent curves are systematically taller and narrower than the first-order profiles predicted from their own Tmax/Cmax. Measured concentrations fall well below the predicted post-peak curves, indicating loss of parent from the plasma compartment beyond simple elimination; given ABX464's neutral logP 6.35 chemistry, rapid partitioning from plasma into tissue is the logical explanation.

The 4 curves from Scherrer 2017 are reproduced digitally (black lines and symbols). The red dot indicates Tmax. We applied a curve fit for a normal first order elimination from the Tmax and Cmax (gray shaded area). The curves do not conform. Parent ABX464 is removed from plasma faster than the first order rates permit. As shown on the plots, the black line falls well under the predicted first order clearance. Rapid tissue uptake of drug from plasma is consistent with these findings.



- ABX464 is a neutral quinoline with a logP of 6.35 and aqueous solubility of 160 nM. It will partition into membrane lipid rather than plasma water.
- The steep decline after Tmax is most likely relocation from plasma into tissues, not clearance.
- The terminal first-order phase is shown in the gray shaded area, the normal distribution built on Tmax/Cmax.

Source: Scherrer 2017a, Antimicrob Agents Chemother 2017;61(1):e01288-16; Scherrer 2017b, J Antimicrob Chemother 2017;72(3):820-828; Scorpion Capital analysis, estimates, and modeling

The same disclosure gap exists for the metabolite N-Glu: ABVX reports a ~4-day half-life while omitting the QD repeat-dose data needed to determine its true accumulation and terminal clearance

N-Glu dominates measured plasma exposure and has a reported 3.8–4.6 day half-life, yet the public repeat-dose record omits complete QD concentration-time curves, clearance and terminal half-life. The published parameters also depart from a simple single-compartment profile, consistent with the slower terminal components identified in our reanalysis.

Abivax reported a terminal half-life of 3.8 to 4.6 days for the N-glucuronide. Food had no effect on exposures. As with parent, no curves for repeated-dose studies or tables with QD repeat-dose parameters were provided for except for the ClinTrials.gov NCT02990325 study (discussed later) comprising AUC, Cmax and Tmax at days 1, 28 and 84 (no half-lives or clearance).

Published PK parameters for parent N-Glu at 50 mg, fasted and fed Roans, across studies, Scherrer 2017b

Study and arm	State	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng·h/mL)	AUC0-∞ (ng·h/mL)	t1/2 (h)	n
Scherrer et al. 2017b, single dose	Fasted	2,627	4	208,811	211,777	97	6
Scherrer et al. 2017a, group 1, single dose	Fasted	2,938	4	203,521	204,112	99.4	23
Scherrer et al. 2017a, group 2, day 1	Fasted	2,127	4	52,858	not reported	not reported	12
Scherrer et al. 2017a, group 2, day 10 Q3D	Fasted	2,314	4	244,320	245,171	101.7	12
Scherrer et al. 2017a, group 1, single dose	Fed	2,752	4	194,661	195,498	100.8	24
Scherrer et al. 2017a, group 2, day 1	Fed	2,475	4	60,092	not reported	not reported	12
Scherrer et al. 2017a, group 2, day 10 Q3D	Fed	3,245	4	325,474	326,237	101.4	12

The published n and mean value for each pharmacokinetic parameter provided by Scherrer 2017a and b.

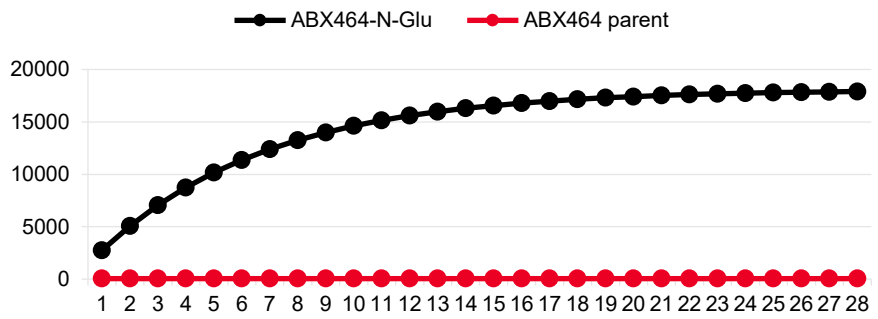
The metabolite to parent Cmax is 160-fold, as reported. These published parameters do not conform to a single-compartment profile for N-Glu as described by the Bateman function (Gibaldi and Perrier, Pharmacokinetics, 2nd ed., 1982). For the metabolite, the reported AUC0-inf was 30 to 53% smaller than Cmax indicating that the terminal elimination half-life did not follow a first-order decline (Scherrer 2017b, Table 4; Scherrer 2017a, Tables 2 and 5).

Source: Scherrer 2017a, Antimicrob Agents Chemother 2017;61(1):e01288-16; Scherrer 2017b, J Antimicrob Chemother 2017;72(3):820-828; Roanes-Lozano et al. 2006; Scorpion Capital analysis, estimates, and modeling

ABVX's published ~101-hour N-Glu half-life predicts ~6.7× accumulation -- but only 1.3× is observed – thus, ~80% of the predicted steady-state plasma exposure is missing, consistent with major redistribution out of plasma and into tissue.

A single dose already produces N-Glu Cmax of ~5.3 µM, approximately the concentration used in many Abivax in-vitro assays. Linear PK predicts steady-state Cmax of ~35.8 µM under QD dosing, yet observed accumulation is only 1.3×. The enormous gap means the drug behaves very differently under repeated dosing than ABVX's single-dose PK predicts; combined with the high V/F and other tissue-partitioning evidence in this section, redistribution into tissue is the logical explanation.

Simulated 50 mg QD over 28 days, single-dose PK from Scherrer 2017



Linear PK accumulation ratio modeled using t½ published by Abivax. R = 1 / (1 − e^(−ln2·24/100.76)) ≈ 6.7×. The gold line shows the predicted accumulation of N-Glu at steady state using the 101h half life is 6.7x.

PREDICTED — LINEAR PK

N-Glu Cmax accumulation: ~6.7×
N-Glu AUC accumulation: ~6.7×
Time to steady state: ~21 days
Parent ABX464 no plasma accumulation: ~1.0×

OBSERVED — NCT02990325 COHORT 3

N-Glu accumulation: 1.3× (Day 1 → 84)
Parent accumulation: 0.49×
5-fold shortfall vs. linear prediction for day 28 exposures.
Both analytes are leaving plasma → possible auto-induction raising levels of an unmeasured metabolite. Without the rest of the data it is impossible to know.

PREDICTED PLASMA LEVELS AT STEADY STATE (Linear PK from Scherrer 2017 fed day 1 parameters)

Analyte (ng/mL)	Day 1 Cmax (ng/mL)	Day 1 $AUC_{0-\infty}$ (ng·h/mL)	SS Cmax (ng/mL)	SS AUC_{0-24} (ng·h/mL)	Cmax ratio	AUC ratio
ABX464 parent	50.21	135.51	~50	~136	**1.0×**	**1.0×**
N-Glu modeled	2,752	195,498	~18,400	~195,498	**6.7×**	**6.7×**

Note: At steady state linear PK, AUC over a dosing interval equals single-dose $AUC_{0-\infty}$. This is a fundamental PK identity. Our simulation is for visualization and verification.
Source: https://doi.org/10.1128/AAC.01288-16; https://clinicaltrials.gov/study/NCT02990325; Scorpion Capital analysis, estimates, and modeling

ABX464's repeat-dose PK changes dramatically over time -- parent exposure falls while N-Glu fails to accumulate as predicted, leaving a large fraction of expected plasma exposure unaccounted for and once again consistent with sequestration into tissue.

By day 28–84, parent AUC falls ~55% while N-Glu rises only ~1.3× versus ~6.7× predicted from its ~4.2-day half-life. The incomplete data provides no repeat-dose half-life or clearance, leaving a large fraction of expected exposure unexplained and confirming that single-dose PK does not describe chronic dosing.

OBSERVED — NCT02990325 COHORT 3 (50 mg QD, n=13, HIV+)

Analyte and measure	Day 1	Day 28	Day 84	Observed fold change Day 1 → 84	Predicted fold change linear PK (last slide)
ABX464 parent AUC (ng·h/mL), 0 - ?	63.7	30.3	28.9	2.2× LOWER	1.0×
ABX464 parent Cmax (ng/mL)	24.5	13.0	15.6	1.6× LOWER	1.0×
N-Glu AUC (ng·h/mL), 0 - ?	11,209.6	13,308.8	14,588.2	1.3×	6.7×
N-Glu Cmax (ng/mL)	2,036.2	1,705.5	2,150.6	1.1×	6.7×

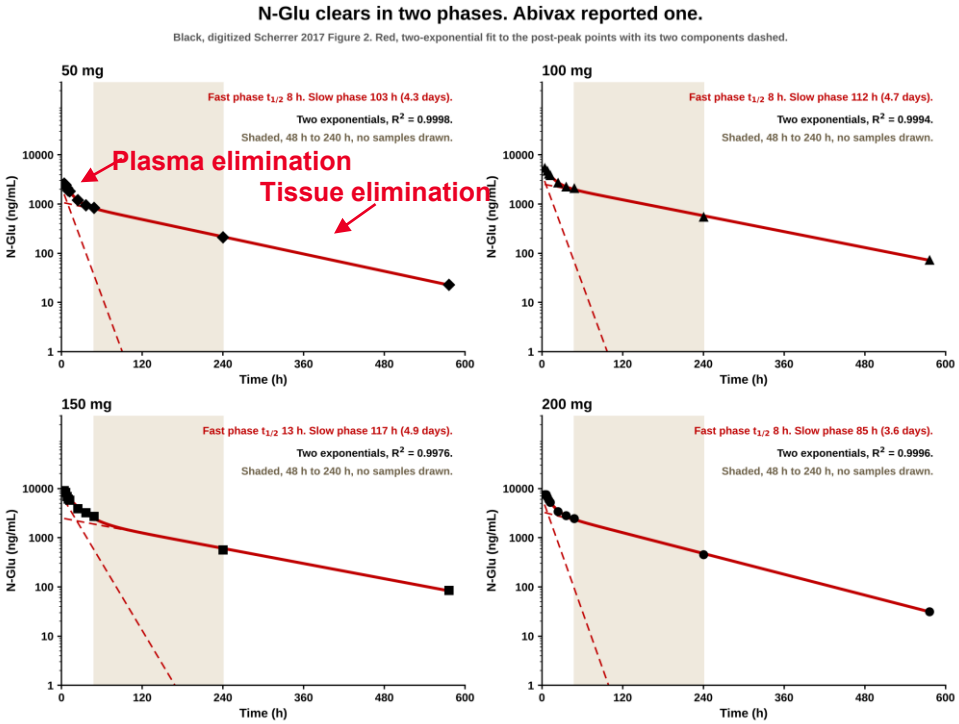
1. The black numbers in the table are Cmax and AUC (Abivax specified no "t") from NCT029990325 ClinTrials.gov . The red numbers are our calculations from those numbers (fold change from day 1) and the calculated accumulation ratio from the 4.2-day half-life (6.7x for N-Glu).
2. Single dose PK predicts ABX464 parent levels should not change between day 1 and day 28. Instead, exposure drops by 50% on day 28 and 84.
3. Similarly, the day 1 parameters for N-Glu predict a 6.7-fold increase in exposure on day 28 vs day 1, and but N-Glu barely accumulates. Pharmacokinetically, a lot of drug is unaccounted for here and we cannot explain this because the datasets are incomplete. Neither half-lives or clearance values are posted, values which would have allowed us to determine if drug clearance had change over time.
4. The Cmax/AUC ratio is commonly used in bioequivalence studies to estimate and compare sampling windows. We calculated the Cmax/AUC ratio with the posted Cmax and AUC values for N-Glu. All 3 cohorts gave ratios indicating an AUC time window of 8h. AUC sampling window (2 50 mg and a 150 mg cohort). The posted exposures appeared to be only about 33% of the 24h convention. We could locate no AUC sampling window on the website or published papers, but it is customary to show a full dosing interval (t = 24h) for AUC0-t. We validated our methods using the parameters and the full datasets from Scherrer 2017 and found the method roughly predicted the known time windows at t = 8 and 24h across datasets.
5. An un-measured metabolite induced by AhR might explain the lack of accumulation, but not lack of first order Cmax/AUC ratiometry. We have no explanation because the data are only partially reported.

Source: https://clinicaltrials.gov/study/NCT02990325; https://doi.org/10.1128/aac.01288-16; Endrényi L, Fritsch S, Yan W. Cmax/AUC is a clearer measure than Cmax for absorption rates in investigations of bioequivalence. Int J Clin Pharmacol Ther Toxicol. 1991;29(10):394–9; Scorpion Capital analysis, estimates, and modeling

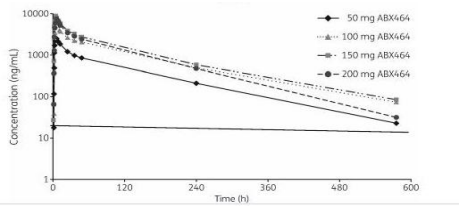
N-Glu's reported ~4-day half-life appears to be the signature of parent drug slowly leaving and leaking out tissue -- not simple N-Glu plasma clearance -- consistent with prolonged parent retention in tissue.

We recomputed Scherrer's plotted datapoints for N-Glu with a 2-compartment model. An unreported early phase was seen cleanly at all four doses (R2 = 0.99). The unreported 8 to 13h early phase suggests renal clearance of N-Glu from plasma and the 4.2-day half-life N-Glu is likely parent slowly leaving tissue.

The plots below show the datapoints from Scherrer 2017 at each of the 4 doses. The black symbols are digitally reconstructed from the original figures at 600 DPI. The red lines show our 2-compartment fit, revealing an undisclosed1 8 to 13h plasma half-life in addition to the reported ~4.2-day terminal phase Abivax reports.



- The 8 to 13h phase clears at 40 to 66 mL/min, a third to half of GFR, consistent with renal elimination of a filtered glucuronide.
- The 4-day phase clears at 5 mL/min, 4% of GFR, too slow for any elimination route, so it is set by the rate parent returns from tissue, not by clearance..
- The volume of distribution for N-Glu is total body water.
- The volume of distribution for parent is 29x total body water which means it is retained in tissues.
- This is consistent with the 4-day elimination phase for N-Glu being limited by parent drug leaving tissues and the parent/metabolite pair being an interconvertible pool.



Original plot, screenshot Scherrer 2017 N-Glu time concentration to 600h

Source: https://doi.org/10.1093/jac/dkw458; Scorpion Capital analysis, estimates, and modeling

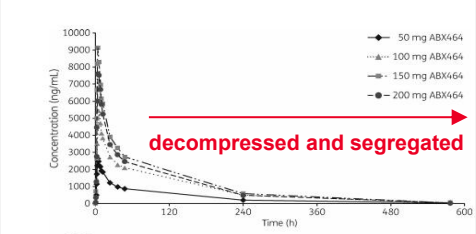
Chapter 10. Obefazimod appears to undergo extensive enterohepatic recycling – repeatedly regenerating parent drug and reloading tissue. We could find no disclosure admitting EHR.

Enterohepatic recycling (EHR) shoulder is seen in every N-Glu PK curve between the 10–12-hour sampling window – slope decrease is inconsistent with first-order elimination

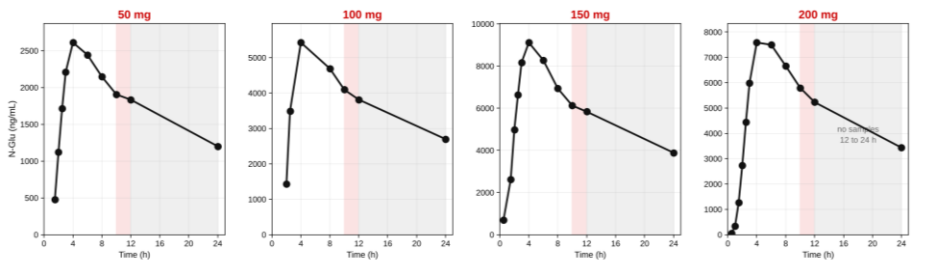
When Scherrer's compressed 600-hour curves are reconstructed over the first 24 hours, all four doses show an unusual flattening between 10 and 12 hours. The four slowest interval slopes all occur in this same window (permutation p=0.003), consistent with a discrete re-entry of drug into plasma such as meal-triggered enterohepatic recycling. Mealtime was undisclosed in the transcript.

A

Compressed original Scherrer 2017

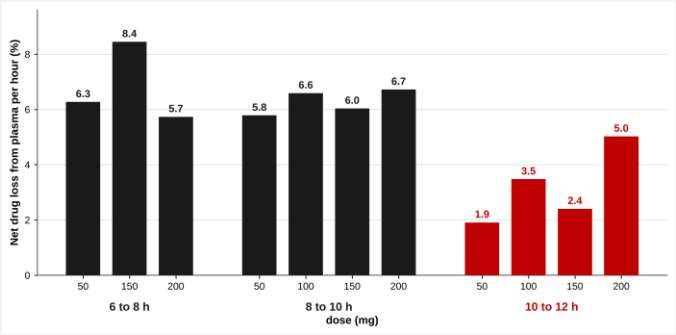


B



Original figure (A) compresses N-Glu time-concentration curves provided in Scherrer 2017b so that the shape of the early phases flatten against the axis (0 to 600h original plot shown in A). We replotted our digital reconstructions out to 24h vs the 600h shown. Method: the points for each dose were digitally reconstructed at 600 DPI and plotted as shown below for each dose (B). We noticed an unusual upward shift in the elimination slope (10-12h) at every dose (pink shading). This would happen by chance about once in 330[1] (permutation test p = 0.003) so it is a significant observation. This shoulder is consistent with drug added back into the blood by enterohepatic recirculation, triggered by a meal-stimulated gall bladder contraction that expels drug into GI where it is deglucuronidated by gut bacteria and reintroduced back into blood. We present this as a finding to be taken in context with all the EHR evidence as shown on the next slide.

C



[1]Eleven windows were measured, three at 6 to 8 h, four at 8 to 10 h, four at 10 to 12 h. Ranked slowest to fastest, the four 10 to 12 h windows occupy the four slowest positions (1.9, 2.4, 3.5, 5.0 percent per hour against 5.7 to 8.4 for the other seven). Under random assignment of timing to rank, the four positions could fall C(11,4) = 330 ways, one of which is all four at the bottom. Exact permutation test, p = 1/330 = 0.003.

Source: Scherrer, J Antimicrob Chemother 2017;72:820-828; Scorpion Capital analysis, estimates, modeling, and interval slope analysis

Six independent PK signals converge on enterohepatic recycling of parent and metabolite – notably, when the biliary recycling pathway is inhibited, N-Glu exposure collapses. EHR massively increases tissue exposure.

Food effect, the long terminal tail, N-Glu dominance, the ~17× ART-associated AUC reduction, the disproportionate AUC-versus-Cmax effect and the reproducible 10–12 h shoulder all point in the same direction. Most strikingly, cobicistat inhibits BCRP-mediated biliary transport and is associated with a far larger fall in N-Glu AUC than Cmax — consistent with disruption of a recycling contribution to exposure..

1. Large food effect
Parent exposure rises 3 to 4-fold. Bile carries N-Glu and dumps it post-prandially.
Bile transit is a key part of EHR.

2. Long terminal t½
4-day terminal phase of a highly lipophilic molecule. EHR prolongs the elimination tail.
Without EHR, glucuronides of this MW should be renally excreted, the shorter 8-13h elimination phase mayrenal .

3. N-Glu is 99.9% of circulating drug
The glucuronide is essentially the entire circulating form. Recycling acts on the high-exposure species. N-Glucuronides structurally similar to ABX464 undergo EHR.

4. AUC of N-Glu 17× lower on ART
Block EHR and, exposure falls. Cobicistat inhibits BCRP, a pump that loads the glucuronide into bile. Blocking that step drops exposure.

5. Cmax ↓5× vs AUC ↓↓17×
Patients on Cobicistat lost 3.5x more AUC than Cmax. Blocking EHR decreases AUC more than Cmax since the loop puts drug back into blood after the main absorption peak.

6. Cmax ↓5× vs AUC ↓↓17×
Plasma loss slows to ~3 percent per hour at 10 to 12 h, against 5.7 to 8.4 percent earlier. First order elimination holds a constant rate, so drug is returning to blood. All four doses show the same shift ($p = 0.003$).

Cobicistat mutes cycling by blocking EHR-dependent biliary transport via BCRP transporter block.

EHR proof #1, recycling likely: MRP2 (ABCC2) and BCRP (ABCG2) pump glucuronides into bile, the first step of enterohepatic recycling. Cobicistat inhibits BCRP, so bile entry is blocked and the cycle stops. AUC falls because less drug cycles back into blood via EHR. Thus, over a 4-day tail the EHR loop recycles with each meal, raising the AUC of the clearance phases by less drug recycled back into blood.

Food effect coupled with parent lipophilicity. AUC fell about 3 times more than Cmax with cobicistat. Cobicistat blocks that and lowers AUC (17x). Cmax is less effected because EHR cycles behind Cmax on the time-concentration curve, elevating the AUC more profoundly than Cmax.

Taken together, we think these findings show N-Glu is cycled by EHR. We can think of no other explanation that fits all six observations.

Source: Scherrer et al., J Antimicrob Chemother 2017;72:820-828, Fig 2. Rutsaert et al., J Virus Erad 2019;5(1):10-22 (ABX464-005); Scorpion Capital analysis, estimates, modeling, and 3-compartment reconstruction

ABX464 and N-Glu appear to behave as one recirculating drug pool -- N-Glu is not simply an eliminated metabolite, but a large active reservoir that regenerates parent and reloads into tissue. We estimate that each molecule of ABX464 converts to N-Glu and back up to 11 times before excretion.

In our EHR model, parent is glucuronidated and circulates as water-soluble N-Glu, then deconjugation regenerates lipophilic parent that repartitions into membranes and tissue before being glucuronidated again. Repeated cycling means the large N-Glu pool contributes to continuing parent exposure and tissue burden rather than representing drug that has already been cleared.

Standard PK assumes the parent forms a glucuronide that the kidney clears. For ABX464, we believe that the glucuronide clears in 2 phases. The early phase represents N-Glu clearing via kidney, most likely and a terminal 4.2h phase from tissues. This makes N-Glu the water-soluble carrier of a drug that is rapidly absorbed back into tissues.



LIVER

~99% of parent glucuronidated on each pass. Plasma fills with N-Glu (40-300x parent).

glucuronidation

PLASMA

Dominated by polar water-soluble N-Glu in TBW.

N-Glu to tissue

TISSUE (the sink)

Beta-glucuronidase convert N-Glu to parent. Parent is reabsorbed into blood and tissues

We believe the parent and metabolite interconvert via EHR. If true, this would mean that:

- ABX464 and N-Glu are one pool, not two. They will interconvert so parent modeling alone vastly understates body burden represented by N-Glu. In this scenario, the N-Glu circulating at 100–300x parent it is a pro-drug reservoir that delivers parent drug to tissues with each conversion.
- Additionally, the N-Glu terminal phase would be parent released from the membrane sink and the may renal N-Glu terminal elimination phase is limited by the rate of parent's slow tissue release.
- For an EHR drug, there is no unique elimination half-life for either form since the drug is stored and shuttled within body compartments. Parent clears into tissues. The glucuronidated form is what finally clears.
- Since the parent is 99% conjugated first pass, the glucuronide is the form that slowly leaves the body.

During each circulatory cycle, N-Glu is taken up from blood into liver and then into gut from the gall bladder. It is held in the gall bladder until a meal stimulates its release into the GI. Gut bacteria cleave ABX464-glucuronide to regenerate parent which is then reabsorbed back into blood where it distributes to tissues.

We estimate that one EHR loop would take about 6 hours, the time between the absorption peak and the secondary (EHR) peak. We further estimate that this cycle occurs roughly 23x on average for a single ABX464 drug molecule.

Source: : https://doi.org/10.1128/AAC.00545-17 ; https://pubmed.ncbi.nlm.nih.gov/12162761/ ; https://www.apotekarsocieteten.se/; Scorpion Capital analysis, estimates, and modeling

ABVX's own protocols appear to quietly flag EHR-relevant drug interactions — yet we could not locate the public studies needed to characterize the recycling pathway. FDA guidance calls for extensive EHR characterization..

FDA/ICH guidance calls for characterization of major metabolites, metabolic pathways, transporters, food effects and ADME where applicable. ABVX's Phase 2b protocol restricts UGT1A9 and OATP1B1/1B3 inhibitors, yet our search of the registry found no applicable UGT/OATP DDI studies, EHR-specific antibiotic or cholestyramine challenge, biliary mass-balance or EHR-specific food-effect characterization.

WHAt FDA REQUIRES FOR PK

- **MIST guidance (2008/2020):** metabolites >10% require characterization. N-Glu = ~99%.
- **ICH M9 / M10:** bioanalytical method validation, LLOQ disclosure.
- **FDA Food-Effect guidance (2022):** food-effect studies for orally administered drugs.
- **ICH M12 Clinical DDI Studies (2024):** CYP, UGT, and transporter DDI characterizations of major metabolic pathways.
- **21 CFR 312.23 (IND content):** full ADME, including biliary excretion.
- **Labeling guidance (2016):** EHR, accumulation, and dose-dependent kinetics must appear in product labeling.

WHAT WE COULD FIND FROM ABVX

- ✓ NCT05121714 — CYP1A2 DDI (caffeine + fluvoxamine). Completed.
- ? 2020-announced ADME study — no NCT per public registry search*
- ✗ No UGT DDI study per our search — despite ABX464-103 protocol prohibiting UGT1A9 inhibitors
- ✗ OATP1B1/1B3 DDI study — despite same protocol prohibiting these\ inhibitors.
- ✗ β-glucuronidase / antibiotic DDI study — the EHR-specific test, run for MMF
- ✗ Cholestyramine challenge — bile acid sequestrant test for EHR.
- ✗ Mass balance with biliary collection
- ✗ EHR-specific food-effect characterization.

Abivax's Phase 2b protocol prohibits UGT1A9 and OATP1B1/1B3 inhibitors as comedications — which we interpret as proof the company knows these interactions are of concern. We could not locate the enzyme characterization studies Abivax would have conducted following FDA guidance that would further inform EHR status.

Sources: https://clinicaltrials.gov/study/NCT03760003 ; https://clinicaltrials.gov/study/NCT05121714 ; https://www.fda.gov/regulatory-information/search-fda-guidance-documents ; https://www.ecfr.gov/current/title-21/section-312.23; *keywords used for registry search to gauge ABVX disclosure - ADME, absorption/distribution/metabolism/excretion · DDI, drug–drug interaction · CYP1A2, cytochrome P450 1A2 · OATP1B1/1B3, organic anion transporter · MIST, metabolites in safety testing · IND, investigational new drug · FDAAA, FDA Amendments Act · CFR, Code of Federal Regulations

Chapter 11. Mass action membrane toxicity and narcosis – obefazimod follows the Meyer-Overton law

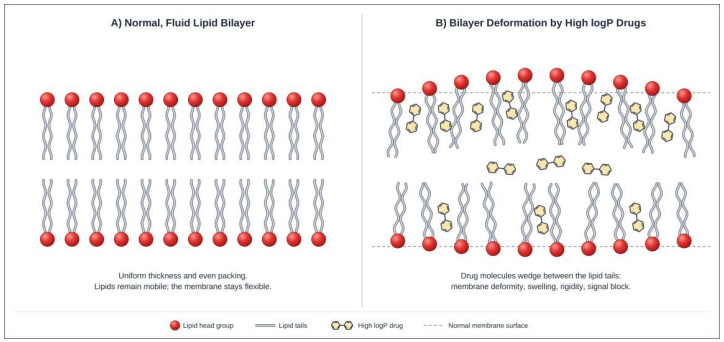
ABX464 behaves as a mass action toxicant – the membrane itself becomes the target -- as demonstrated in vitro (cell assays), in vivo (C. elegans motility), and arithmetically. Narcosis is driven by membrane concentration of the drug (50 mmol/kg lipid), independent of species or cell type.

1. The critical membrane threshold (CMT) is the same membrane concentration across species and cell type.

Mass action drugs are notoriously nonspecific, since the "target" is the membrane itself. The critical membrane threshold (CMT) is 50 mmol/kg across fish, Daphnia, bacteria and mammalian cells. We could find no record of specificity screens, the kind a contract research organization such as Eurofins commonly runs before first-in-man studies. These are generally disclosed far before Phase 3 studies along with transporter and metabolic enzyme panels. Our examples show two comparator compounds like ABX464 (high logP, planar, phototoxic, active against DSS colitis) collectively inhibit 26 unrelated cell proteins (next slide).

2. Mass action has no target, the membrane is the target

At CMT the cell membrane is filled with drug: docking sites warp, and fluidity changes. The membrane disorders and interferes with signaling functions, channel opening and transport protein shuttling. Mass action is a well-studied anesthetic mechanism as well. Cell signals that run through membrane lipid intermediates, such as PI3K and AKT, are susceptible to block. In fact, mass action may be the mechanism of the PI3K/AKT block, observed with ABX464.



A normal bilayer on the left. On the right the same bilayer carrying drug at saturation shows swelling, curvature and loss of order. Original diagram, Scorpion Capital LLC.

3. For mass action there is no safety margin.

For a mass action drug, the effective concentration is the toxic concentration. A dose-response is likely a function of distribution pharmacokinetics; like the dose-related headache, pancreatic acinar leak, and hepatotoxicity signals seen across clinical trials. In contrast, responses in GI are maximal and equivalent across doses within weeks of dose initiation.

We infer the drug may activate a receptor in addition to mass action block. ABX464 is reported to be an AhR agonist, a property we confirmed in our audit, undisclosed by ABVX per our search. The signaling pattern and target organ toxicity are expected for a logP 6.35 mass action drug. We see no safety margin from our audit of the program.

4. Planar mass action drugs produce cytotoxicity, not lysis.

Mass action drugs that cause cytolysis are too toxic to be of therapeutic interest but ABX464 belongs to a class of planar neutrals that lie between the lipid tails. ABX464 has an –OCF3 group that is predicted to anchor it deep in the bilayer core as shown above. Drugs like this become a part of the membrane but not in a good way.

Above the CMT membranes swell and disorder, membrane proteins crowd, cell signaling degrades and mitochondrial ATP output falls. The effect depends on membrane concentration, not on a binding pocket. A mass action drug may blunt signaling without binding the protein, because it changes the protein environment.

Sources: Könemann 1981; van Wezel & Opperhuizen 1995; Yalkowsky & Valvani 1980; OECD Test Guideline 117; Scorpion Capital, logP pKa report and lab experiments; Bowes et al. 2012; Lynch et al. 2017; Wang et al. 2025; Scorpion Capital literature/publication review, estimates, analysis, and modeling

ABX464 resembles promiscuous mass action anthelmintics – but is orders of magnitude more lipophilic, worsening the same broad off-target liability. Mass action compounds hit lots of unrelated proteins, and ABX464 has an even more extreme partitioning profile.

ABX464 has similar chemical properties to curcumin and niclosamide. These examples collectively inhibit 26 functional proteins. By inference, we expect ABX464 to have multiple off-target effects; we only found evidence of AhR agonism and PI3K block occurring at 5 μµM. Like ABX464, curcumin and niclosamide circulate as predominant glucuronides, cycle by enterohepatic recirculation (EHR), and are active in DSS colitis mice. Curcumin and ABX464 are both photoactive, and niclosamide is a photooxidizer. All are autofluorescent. All three function by mass action narcosis. Many off-target effects are expected, and all will initiate together at narcosis baseline. Like ABX464, both have been in human trials for ulcerative colitis. Mass action agents are generally too toxic for long term therapeutic use, and these programs were terminated. Niclosamide is approved as a short-term anthelmintic. Relevant safety studies are not disclosed in our searches in any detail to confirm or refute our hypothesis.

Comparator anthelmintics against ABX464 show remarkable similarities. ABX464 is orders of magnitude more lipophilic.

Compound (logP)	Dominant circulating glucuronide	EHR	DSS colitis	Phototoxicity	Prescribed in humans	Anthelmintic	Last clinical phase and status
Curcumin (4.1)	Yes	Yes	Active	Phototoxic	No	not reported	Phase 2/3, ulcerative colitis, abandoned, too hepatotoxic for clinical use
Niclosamide (4.5)	Yes	Yes	Active	Photoactive, photooxidizes	Yes, as an anthelmintic	Yes, approved	Phase 1, ulcerative colitis, abandoned, used short term for de-worming
ABX464 (6.35)	Yes	Yes	Active	Photoreactive	Ongoing trials	Yes, C. elegans, H. contortus	Phase 3 ABTECT, ulcerative colitis, ongoing

These chemically similar anthelmintics act by mass action membrane narcosis and block many functional proteins:

CURCUMIN logP 4.1 18 proteins affected

Transporters (10). ABCB1 (P-glycoprotein), ABCG2 (BCRP), ABCC1 (MRP1), ABCC2 (MRP2), ABCA1, GLUT1, GLUT4, organic anion transporters, organic cation transporters, URAT1 (urate transporter)

Ion channels (5). CFTR, voltage-gated potassium (Kv), high-voltage-activated calcium, volume-regulated anion channel, calcium release-activated calcium channel

Water channel (1). Aquaporin-4

Nuclear receptor (1). Farnesoid X receptor

Enzyme (1). Xanthine oxidase

NICLOSAMIDE logP 4.5 8 proteins affected

Transporters (5). OATP1B1, OATP1B3, OAT1, OAT3, OCT2

Ion channels (3). TMEM16A and TMEM16F (calcium-activated chloride channels controlling artery tone and capillary diameter), CFTR

Sources: Marafini et al. 2024; Kumar et al. 2012; Ben-Horin et al. 2024; Dahl et al. 1994; Chignell et al. 1994; Natera et al. 2015; Shanley et al. 2024; Scherrer et al. 2017; NCT02990325; Alghzawi et al. 2024; Abdallah et al. 2020; Scorpion Capital literature/publication review, estimates, analysis, and modeling

ABX464 obeys the Meyer–Overton law: potency rises with lipophilicity, the classic signature of mass-action membrane narcosis. The test has been used since 1899 to demonstrate membrane narcosis. It has a definitive linear signature -- ABX464 conforms by two assays and a calculation.

THE MEYER-OVERTON LAW

- Meyer (1899) and Overton (1901) demonstrated that anesthetic potency was proportional to lipid solubility across all chemical classes tested. They found potency was log-linear in proportion to logP, a straight line across 4 to 5 orders of magnitude.
- When cell membrane concentration reaches ~50 mmol/kg the cell undergoes narcosis or mass action shift. Membrane partitioning (lipophilicity) is what dictates drug potency/toxicity.
- Above a critical logP, insolubility holds membrane equilibrium below the narcotic concentration.
- Below a critical logP drug dissolves and remains in the water phase, so the membrane threshold is not possible at peak solubility. Proteins and matrix attachments will raise the apparent nominal concentrations.
- Mass action is independent of structure. Any drug that saturates membranes at ~50 mmol/kg will produce narcosis.

THE LAW AND ABX464

- **Activity tracks lipophilicity.** Increasing logP increases potency in a log-linear relationship. Above the threshold narcotic effects may increase in severity and diversity until solubility limits are reached in the aqueous phase (7.2-fold over threshold for ABX464). Protein will buffer and shift the apparent concentration higher in cell vs motility assays.
- **Nonselective.** Membranes have the same lipophilic character across all cell types in the animal kingdom.
- **No stereochemical selectivity.** Mirror isomers are equipotent. (ABX464 has no chiral center).

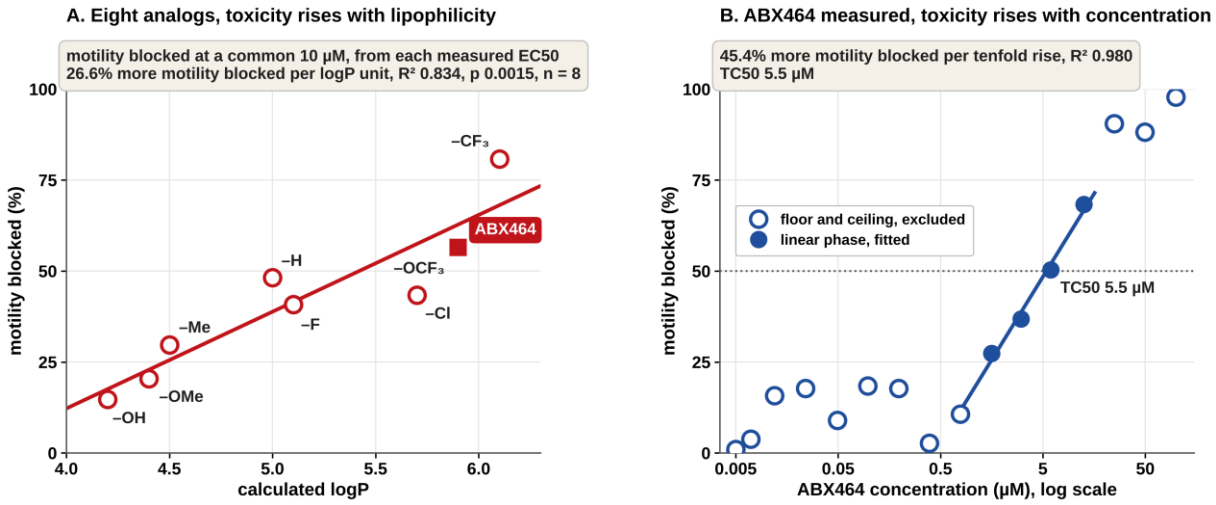
The Meyer-Overton law is demonstrated in C. elegans and human PBMCs (next slides).

Shanley et al. 2022 obtained ABX464 from the Pandemic Response Box library of possible anthelmintics. ABX464 was active against C. elegans. Several anthelmintic drugs act by mass action to inhibit the ion channels necessary for worm motility. Shanley synthesized eight analogs on the ABX464 2-arylaminoquinoline scaffold, varying the R1 substituent. Potency against C. elegans motility was linear against logP with R^2 0.834 ($p = 0.0015$, $n = 8$) for all eight analogs, including ABX464. ABX464 is active in both nematodes and human cells.

Sources: Lipnick 1989; Shanley et al. 2024; Shanley et al. 2022; Meyer 1899, Arch Exp Pathol Pharmakol 42:109-118; Overton 1901, Studien über die Narkose; Scorpion Capital literature/publication review, estimates, analysis, and modeling

ABX464's structure-activity passes the Meyer–Overton test twice -- toxicity rises linearly with both lipophilicity and concentration/dose, without receptor-like saturation or Hill slope that a receptor interaction would show. This is mass action defined.

The red plot shows ABX464 and its analogs conform to the Meyer-Overton law (A). We calculated logP from the published structures and used the value for ABX464 from the same in silico method. LogP was plotted against the activity reported in the manuscript. The dose-response curve was digitally reconstructed at 600 dpi (B) from the original figure. LogP values were calculated by the Hansch/Leo and Crippen methods, summing hydrophobic contributions of the quinoline scaffold and the substituent, with a correction factor of 1 applied to align calculated values with measured logP.



R1 was varied across compounds and graphed against logP (A); in (B) concentration was plotted against parasite toxicity.

Panel (A) shows potency increases (motility block in C. elegans) linearly with logP (R^2 0.834, p = 0.0015, n = 8) for the ABX464 analogs. Panel B shows ABX464 activity in C. elegans is linear with concentration (R^2 0.980), with a TC50 of 5.5 µM, and no plateau (B).

These concentrations in the worm are toxic concentrations as the readout was worm mobility. C. elegans is reported to be a better method for estimating in vivo toxicity than cytotoxicity assays. The TC50 for ABX464 is near where Abivax conducts all its cellular assays.

The structure-activity correlation with logP was linear. The dose-response "curves" were also linear. A receptor-mediated event would saturate. Human cells show the same linear dose-response (next slide).

Baseline toxicity is not a switch for ABX464 but rather a graded event above threshold. Membrane loading will increase past CMT with mass action effects worsening in concert, until the free solubility limit is reached.

For ABX464 that ceiling is a membrane concentration of 0.358 mol per kg lipid or about one drug molecule to 4 lipids. ABX464's solubility ceiling is 7.2-fold above its narcotic threshold.

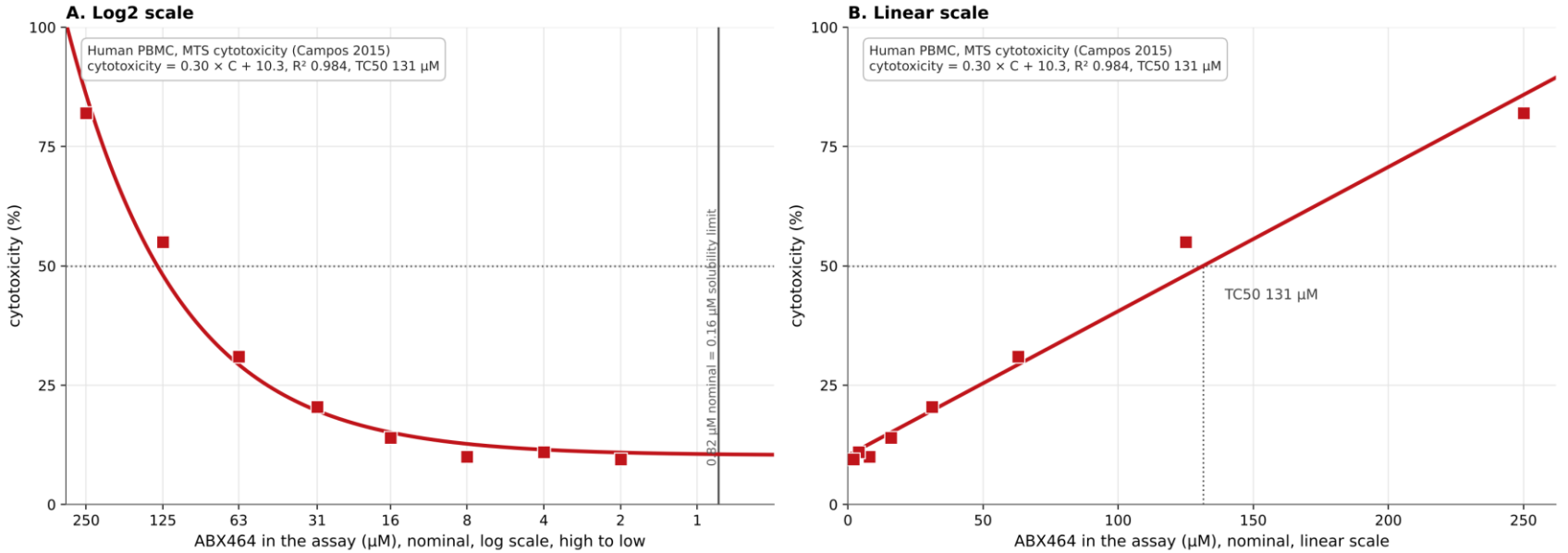
GI membrane saturation is estimated at 295 µM[1] (25 mg dose) consistent with the lack of dose or time-response in the clinical GI endpoints.

1. A 25 mg dose is 74 µmol (25 mg ÷ 338.72 g/mol). In 250 mL of luminal fluid (Amidon et al. 1995) that is 295 µM, 1,844 times the 0.16 µM aqueous solubility and 546 times the 0.54 µM lowest concentration that produced measurable toxicity.

Sources: Shanley et al. 2024; Shanley et al. 2022; Scorpion Capital, logP pKa report and lab experiments; Hunt 2017; Williams & Dusenbery 1988; Amidon et al. 1995; Scorpion Capital literature/publication review, estimates, analysis, and modeling

The same mass-action signature appears in human cells -- ABX464 cytotoxicity is linear with concentration across a 125-fold range, no plateau.

Campos et al. 2015 Figure 1c reports MTS cytotoxicity in human peripheral blood mononuclear cells (PBMC) across 2 to 250 µM nominal. We digitized the Campos dataset and replotted it. Panel A reproduces the unusual reversed log2 layout the manuscript used, with the original figure inset. Panel B replots the same eight means on a conventional linear axis running low to high.



Cytotoxicity is a linear function of concentration: 0.30 × C + 10.3, R² 0.984, across the full 125-fold range.

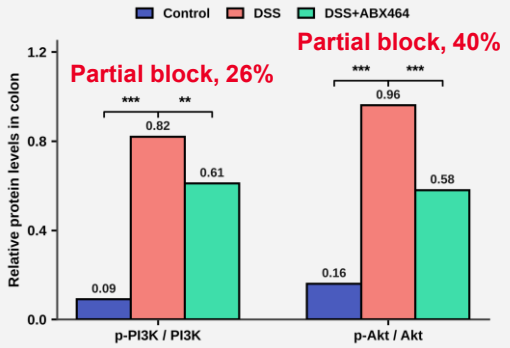
A receptor-mediated effect saturates with receptor occupancy, creating an asymptotic curve. In contrast, ABX464 produced a straight dose-response, the same mass action function observed in the nematode. We found the concentration measured in this assay to be 5-fold below the nominal concentrations reported. The assays were conducted in 10 percent fetal calf serum, and serum proteins bind drug to decrease the free concentration further, shifting the human curve to the right. Our DLS studies showed that albumin carries ABX464, though we were unable to quantitate protein binding (Scorpion Capital, DLS and autofluorescence report, 2026). All eight assay concentrations were above both ABX464's solubility and the critical membrane threshold (CMT). No concentration was non-toxic as the lowest concentration was at 9.5% cytotoxicity MTS. Tazi's group reported that ABX464 was safe under 60 µM from these data, a concentration corresponding to 28% cytotoxicity by their nominal values. Campos observed that the drug formed aggregates that led to "some toxicity to the cells", so they centrifuged out the drug and reported nominal concentrations (cytotoxicity section). We show this here to demonstrate Meyer-Overton in human cells.

Sources: Campos et al. 2015; Scorpion Capital, cytotoxicity and clinical findings report, 2026; Scorpion Capital literature/publication review, estimates, analysis, and modeling

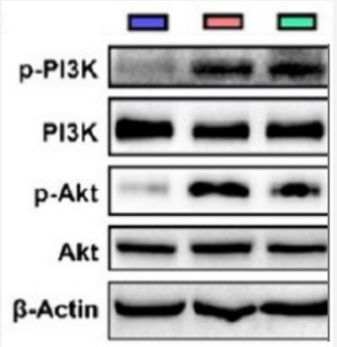
ABX464 directly blocks PI3K/AKT in the DSS colitis model (Wang, 2025) -- consistent with mass-action membrane toxicity, not the purported selective miR-124 upregulation mechanism. No human AKT data were presented, but a mass action-mediated AKT block would be species agnostic.

Novel Small-Molecule miR-124 Inducer Acts as "a Physiological Brake" of Inflammation in Ulcerative Colitis by Targeting the PIK3R2/PI3K/Akt Axis (Wang, 2025)

A. Mean phosphorylation ratios of PI3K and AKT from mouse colon homogenates



A. Representative Western blot



DSS-associated PI3K activation suppressed 26% ABX464

PI3K protein, no change

DSS-associated AKT activation blocked 40% by ABX464

AKT protein, no change

Loading control β-actin, no change

P values are ANOVA followed by Tukey's multiple comparison test. Data are from the original figure extracted as exact pixels at 400 DPI for the selected sections. The full dataset is available as cited. The interpretation is ours. "A" shows mean ratios from densitometry. "B" shows a representative Western blot.

Method and conclusions

- Healthy control mice were given water (blue) and DSS groups drank 3% dextran sulfate sodium for 8 days to induce colitis. Vehicle (orange) or ABX464 (green), 50 mg/kg QD, oral administration.
- Colon tissue was homogenized and proteins were sorted by size on a 10% SDS-PAGE gel, and proteins were transferred to a PVDF membrane for antibody tagging and visualization. Band density was measured by ImageJ and normalized to β-actin. A representative blot is shown above.
- Panel "A", bar graph of mean ratios (phosphorylated to unphosphorylated AKT and PI3K).
- Panel "B" a representative Western blot.
- We used the authors' statistics as presented in Wang 2025.
- ABX464 blocked the phosphorylation of PI3K by 26% ($p < 0.01$) and Akt by 40% ($p<0.001$) compared to vehicle.
- The phosphorylated forms are the active forms. **These data demonstrate that ABX464 significantly blocked activation of the PI3K/Akt pathway in mouse colon.**

Sources: Wang et al. 2025, J Med Chem 68(13):14114-14126; Scorpion Capital literature/publication review, estimates, analysis, and modeling; figure redrawn from Wang 2025, Figure 5B and 5C -- some data are omitted for clarity; bands are digitized from Figure 5C; significances are as reported.

ABVX's own antifibrotic assay (ECCO 2026) points back to PI3K/AKT blockade without naming the pathway directly -- ABX464 tracks a known PI3K/AKT inhibitor.

AKT blocker was chosen as the positive control

"Obefazimod shows first evidence of anti-fibrotic activity in preclinical models of inflammatory bowel disease" (Danese et al, 2026 – ECCO poster)

Human small-intestinal fibroblasts model, the three comparators:

1. **Omipalisib, pan-PI3K/AKT inhibitor.**
2. **Nintedanib VEGFR/FGFR/PDGFR inhibitor.** Approved as Ofev for pulmonary fibrosis.
3. **Upadacitinib JAK1 inhibitor.** Marketed as Rinvoq for UC and Crohn's.

- **The methods refer to "mechanistic comparators"**
- **The footnote identifies omipalisib by indication, rather than its mechanism, "in development for IPF & oncology indications."**

Abivax reports "the pathway" enigmatically

Nintedanib was inactive (antifibrotic).

Omipalisib was active (AKT blocker).

Obefazimod and omipalisib inhibited collagen output ~50%, roughly similar magnitude.

The ECCO abstract states:

"Notably, [in] the IBD-FC SiaJ assay [ABX464] showed pathway specificity: nintedanib showed no activity, while omipalisib did."

- The specificity is attributed to the assay. The pathway is not named. The bracketed inserts we added are implied by the context.
- The sponsors name no pathway in this poster, neither JAK1 nor AKT, while the JAK1 pathway is named >20 times in other posters.

WANG 2025 shows ABX464 blocks AKT

An independent group, funded by the National Natural Science Foundation of China (grant 82400609), declaring no competing financial interest, shows AKT block by ABX464.

Female mice, colon immunoblots: p-PI3K/PI3K falls 26% and p-Akt/Akt falls 40% against vehicle. Thus, ABX464 blocked both phosphorylation events.

"FHND5032 exhibited a stronger inhibitory effect on … the PI3K/Akt pathway compared to that of ABX464 in vitro."

The comparison acknowledges that ABX464 blocks PI3K/AKT while pointing out their drug is better.

FHND5032 is ABX464 with two changes, a nitrogen for carbon substitution on the pyridine ring of the quinoline and the chlorine moved from position 8 to 7.

Our AKT/PI3K inference – summary and sources

1. **Omipalisib is a published pan-PI3K/AKT inhibitor, GSK2126458. Abivax uses the drug in their assay without naming its mechanism.**
2. **Abivax asserts that the assay has pathway specificity. Two out of three compounds are active, ABX464 and the AKT blocker. The PI3K/AKT pathway is therefore inferred by the published target to be AKT block.**
3. **Nintedanib was inactive and omipalisib was active. The assay was touted as an antifibrotic assay, but the approved antifibrotic drug (Nintedanib) failed, which invalidates the poster's banner claim of "anti-fibrotic activity". It follows that the same AKT pathway is affected by ABX464.**
4. **Obefazimod and omipalisib exhibited similar magnitudes of pro-collagen inhibition, consistent with a shared mechanism.**
5. **Wang 2025 measured PI3K/AKT block directly in mouse colon and states their drug superior against ABX464, naming drug and pathway in the same sentence.**
6. **Abivax has neither confirmed nor denied AKT block; our searches turned up zero hits for AKT and associated terms.**

Mass action and AhR activation may have opposing effects on AKT: AhR increasing it and AKT block decreasing it.

AhR activation by ABX464 is demonstrated at the concentrations tested, and AhR activation increases PI3K and AKT signaling. Mass action may blunt AKT activation and would physically trump AhR's input at that junction. Thus, AhR activation signals that run via AKT, like the noninduction-mediated IL22 elevation and mitogenesis, might be lower than expected compared to AhR agonists exhibiting no mass action effects.

The quoted sentences are reproduced as published except where bracketed. PRO-C3 values were digitized from DDW Figure 3 at 500 DPI against the printed axis ticks. Wang percentages are the authors' reported reductions against vehicle. A literal text search of 67 Abivax corporate and conference documents (658,270 characters) and 14 primary Abivax and Tazi papers (727,821 characters) returned zero instances of PI3K, AKT, Akt and mTOR. The AhR EC50 of 404 nM is from a HepG2-Lucia reporter assay reported by Equillium, 27 May 2026. Omipalisib (GSK2126458) is a pan-class-I PI3K and mTOR inhibitor, which blocks AKT signaling.

Sources: Danese et al. 2026 (ECCO OP30); Danese et al. 2026 (DDW Tu1433); Wang et al. 2025; Equillium 2026; Shi et al. 2021; Scorpion Capital literature/publication review, estimates, analysis, and modeling

Chapter 12. Cytotoxicity, slowed cell division, mitochondrial failure -- ABVX's "non-toxic" claims collapse under scrutiny

ABVX's "non-cytotoxic" claim is repeated across its papers and materials, but ultimately traces back to just one key paper -- Campos 2015. Later ABVX/Tazi publications recycle that conclusion rather than independently establishing it. The rest of this chapter shows that the underlying Campos assay is deeply compromised and, once corrected for actual drug exposure, shows substantial cytotoxicity across the tested range. We also present our own LC-MS/MS experiment, which directly contradicts ABVX's purported safety threshold.

ABX464 is declared non-cytotoxic and non-mitotoxic in publication after publication, but ABVX's claim ultimately traces back to the Campos assay. Shanley et al. are independent researchers; their own published data provide separate evidence of mitochondrial toxicity.

Campos et al. 2015 (Abivax, Tazi senior author)	Apolit et al. 2023 (Abivax, Tazi senior author)	Shanley et al. 2022 and 2024 (independent)
Retrovirology. The source of the claim	*Clin Transl Gastroenterol. Figure legend*	*University of Melbourne. No Abivax affiliation.*
Quotes from the manuscript **Abstract.** *"Consistently ABX464 is non-toxic in humans and therefore represents a promising complement to current HIV therapies."* **Results heading, no reference given.** *"ABX464 is readily metabolized and is non-toxic"* **Results, PBMC assays.** *"ABX464 is only toxic at doses higher than 60 µM but has no effect on cell proliferation."* **Results, macrophages.** *"However, cell viability was not decreased under ABX464 treatment (data not shown)."* **Discussion.** *"ABX464 is globally not toxic to infected cells…"* **Methods, value not reported.** *"The TC50 was calculated by regression to determine the compound concentration responsible for 50% of cytotoxicity."*	**Quote from the manuscript** **Figure legend.** *Cells were treated for 6 days with concentrations held below a stated ceiling "to avoid a cytotoxic effect."* The ceiling is stated without a supporting assay. Abivax ran one cytotoxicity assay, the MTS test in Campos Figure 1c. The flow cytometry panels are reported "among viable CD4+ cells," therefore cells lost to the drug leave the denominator. Neither a cell count nor a viability dye appears in the paper.	**Quotes from the manuscripts** **2022, concerning ABX464.** *"Neither cytotoxic (CC50 ≥ 100 µM) nor mitotoxic (MC50 = 81.1 µM) against HepG2 human hepatoma cells"* **2024 SAR, five analogues, not ABX464.** *"None of these compounds were found to have human cell cytotoxicity (CC50 ≥ 40 µM) or mitotoxicity (MC50 ≥ 40 µM)."* **2024 target paper, no assay run.** *"Both ABX464 and compound 36 have been previously found to be non-cytotoxic and non-mitotoxic to human hepatoma (HepG2) cells"* **A finite MC50 of 81.1 µM is a measurement of mitotoxicity. The 2024 range stops at 40 µM, half that concentration.**

Sources: Campos et al. 2015; Apolit et al. 2023; Shanley et al. 2022; Shanley et al. 2024, SAR; Shanley et al. 2024, target; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Campos, Tazi et al. claim "ABX464 is readily metabolized and is non-toxic," yet their own 28-day monkey toxicology study stopped dosing early in every treated group and sacrificed moribund animals -- difficult to reconcile with the claimed NOAEL. Dosing was stopped by day 10 of a planned 28-day study for half the treated animals, none continued past day 18, and 20–30% of animals in several dose groups were sacrificed moribund.

Campos (2015): "In non-human primates, the main target organ of ABX464 toxicity was found to be the gastro-intestinal tract. The NOAEL was considered to be 250 mg/kg b.i.d (Additional file 2: Table S1)."

Definition, moribund: "*In a state of dying, from which recovery is not expected. In toxicology an animal is classified moribund when clinical signs indicate that death is imminent and irreversible, for example loss of righting reflex, inability to reach food or water, severe weight loss, hypothermia, or unresponsiveness to stimuli. The animal is then killed rather than left to die.*"

Abivax claims a NOAEL of 250 mg/kg despite 20–30% of animals becoming moribund in multiple treated groups, including at the lowest tested dose. No treated group was able to complete the planned 28 days of dosing. Those findings are difficult to reconcile with a "no observed adverse effect" designation.

Dose group	Animals (n)	Last day of dosing	Moribund sacrifices (n)
Control	5M/5F	NA	0
75 mg/kg b.i.d.	5M/5F	Day 18	2[1]
250 mg/kg b.i.d.	5M/5F	Day 18	2 (Claimed NOAEL)
750 mg/kg b.i.d.	5M/5F	Day 10	3
1,500 mg/kg s.i.d.	5M/5F	Day 10	Dosing stopped day 10

1. Design as reported: 25 females and 25 males, 5 per sex per group, 4 weeks of dosing with a 3-week follow-up. Dosing was stopped at day 10 for dose-levels at or above 750 mg/kg and at day 18 for the lower dose-levels, "due to poor clinical condition of the animals", which is vague.
2. [1]The source reads "sacrifice of 3 moribund animals at 750 mg/kg b.i.d. (day 9 and 14) and 2 moribund animals at 250 and 75 mg/kg b.i.d. (day 15)".
3. The dosing stops at day 10 for "dose-levels ≥ 750 mg/kg". \
4. Doses are as reported in the source, which does not state whether the figure is per administration or per day. The same table states a NOAEL of 250 mg/kg/day b.i.d. It cannot be both.

Sources: Campos et al. 2015, Additional file 2: Table S1; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX conducts most of its in vitro assays at a single 5 µM concentration. We demonstrate that this favored assay concentration is 12.8-fold above the cytotoxicity threshold, 31-fold above water solubility, and directly in the aggregate-to-crystal transition window – undermining its central mechanistic "evidence."

Thus, the resulting readouts cannot be distinguished from nonspecific cytotoxicity and aggregation artifacts, rather than establishing selective miR-124 upregulation – the very concentration used to demonstrate the purported mechanism is already in the cytotoxic range.

Membrane narcosis, cytotoxicity and aggregation artifact will influence assay readouts at 5 µM. This is the concentration at which ABX464 forms crystals in our autofluorescence studies. Each readout is a downstream consequence of the same physical chemistry: AKT block, membrane narcosis, AhR activation or cytotoxicity. Of the 23 assays we surveyed, only the cytotoxicity assay carried a cytotoxicity or viability metric. There we showed by LC-MS/MS that actual concentrations ran 5-fold lower than nominal, and cytotoxicity was measurable from 0.39 to 20 µM actual.

Assay / readout	Source
Rev/HIV RNA splicing (p24 suppression)	*Campos 2015*
Western blots AKT phosphorylation block*	*Wang 2025*
PBMC cytokine panel (Luminex bead array)	*Apolit 2022*
PBMC Th17 FACS (cekytotoxicity)	*Apolit 2022*
CD4+ T cell IL-17a (aggregation artifact)	*Apolit 2022*
Macrophage cytokine suppression (cell death)	*Chebli 2017*
UV crosslinking "CBC binding" (aggregation)	*Campos 2015*

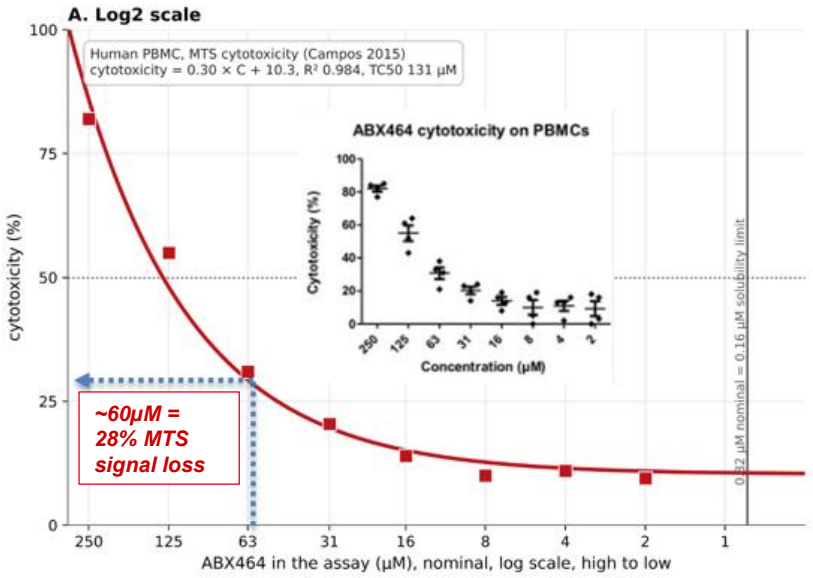
Assay / readout	Source
C. elegans motility IC_{50} (mass action TC_{50})	*Shanley 2024*
miR-124 qPCR in HeLa (no upregulation)	*Chebli 2017*
Caco-2 barrier FITC-dextran permeability	*Wang 2025*
Macrophage phagocytosis of drug aggregates	*Apolit 2022*
CYP1A1 27.7-fold induction (AhR xenobiotic)	*Chebli 2017*
Cytotoxicity assay (drug centrifuged out)	*Campos 2015*
Bone marrow macrophage TNF-α collapse	*Chebli 2017*

Aggregation and cytotoxicity are poorly controlled in vitro, and both are the most common artifacts observed. Abivax routinely conducts their in vitro assays at cytotoxic concentrations without viability controls or cell counts (Campos 2015, with our LC-MS/MS actual concentrations).

Sources: Könemann 1981; van Wezel and Opperhuizen 1995; Yalkowsky and Valvani 1980; OECD Test Guideline 117; Helander and Fändriks 2014; Campos et al. 2015; Scorpion Capital log P and pKa report; Scorpion Capital DLS and autofluorescence report; Scorpion Capital cytotoxicity and clinical findings report; Scorpion Capital literature review, research, estimates, analysis, and laboratory experiments

ABVX's sole cellular cytotoxicity assay contradicts its claim that ABX464 is "non-toxic below 60 µM" -- at ~60 µM, the assay's own MTS readout has already fallen ~28%. Whether that loss reflects cell death, metabolic suppression or both, a 28% reduction is a substantial adverse cellular effect, not "no effect." More importantly, the assay never identifies a non-toxic threshold: a measurable cytotoxicity signal is present even at the lowest concentration tested.

Campos 2015 PBMC cytotoxicity assay — the concentration called "non-toxic" already produces a ~28% loss in MTS signal.
Chart source: Campos et al. (2015), Fig. 1c; digitized and replotted by Scorpion Capital. Original figure shown inset.



Methods

Human PBMCs were exposed to nominal ABX464 concentrations for 6 days and assessed with an MTS metabolic-activity assay. We digitized Campos Fig. 1c and replotted the reported mean values (in red). The original data are shown as an inset.

Why The Assay Does Not Support "NON-TOXIC"

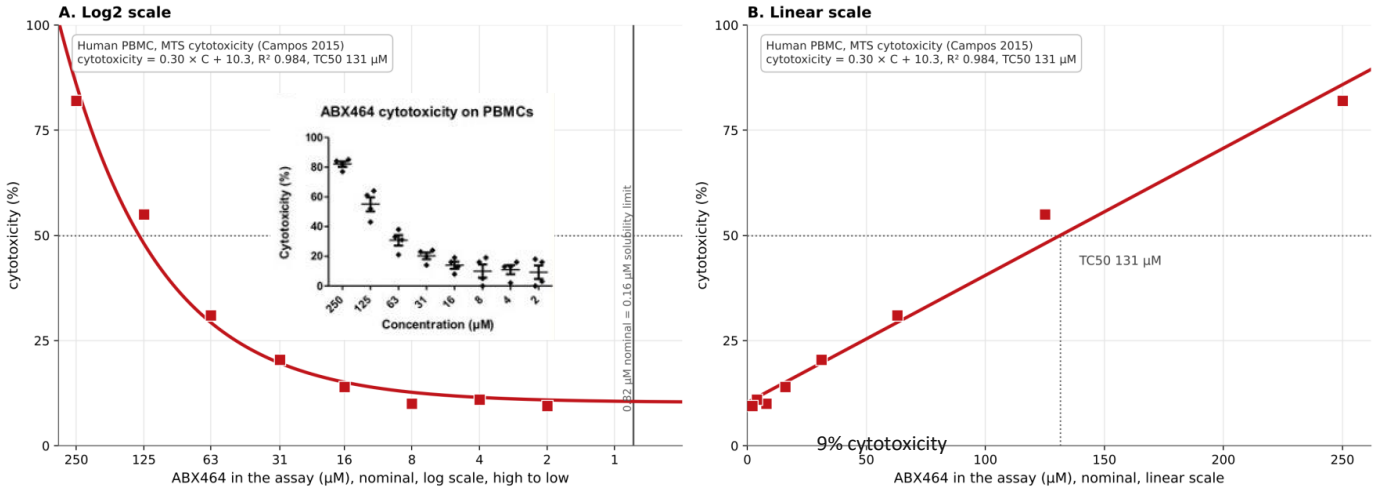
- **The claimed safe concentration already shows a large effect: at 60 µM, the published curve indicates ~28% loss of MTS signal.**
- **MTS is not a direct cell count: the 28% decline could reflect fewer viable cells, lower metabolism per cell, or both.**
- **This is ABVX's only reported cytotoxicity assay in the preclinical corpus we reviewed.**
- **The reversed log2 axis visually compresses the concentration-response. Replotted conventionally, the next slide shows no evident safe plateau.**
- **The paper says a TC50 was calculated but does not report it. From the published nominal-concentration curve, we calculate ~131 µM.**

Campos et al. (2015): "ABX464 is only toxic at doses higher than 60 µM but has no effect on cell proliferation." Yet at ~60 µM, the same paper's MTS cytotoxicity curve already shows ~28% signal loss. The paper also acknowledges that ABX464 "forms aggregates when applied directly to cell cultures, which leads to some toxicity to the cells."

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABX464 has no experimentally demonstrated non-toxic concentration in this assay -- cytotoxicity is measurable even at the lowest concentration tested. We replotted conventionally from low to high on a linear scale and the supposed safe plateau disappears: cytotoxicity rises linearly with concentration, with ~9% already present at the lowest dose tested. The resultant straight line is consistent with cytotoxicity driven by mass-action partitioning rather than a discrete toxicity threshold.

Campos et al. 2015 Figure 1c reports MTS cytotoxicity in human peripheral blood mononuclear cells (PBMC) across 2 to 250 µM nominal. Panel A reproduces the unusual reversed log2 layout the manuscript used, with the original figure inset. Panel B replots the same eight mean concentrations on a conventional linear axis running low to high.

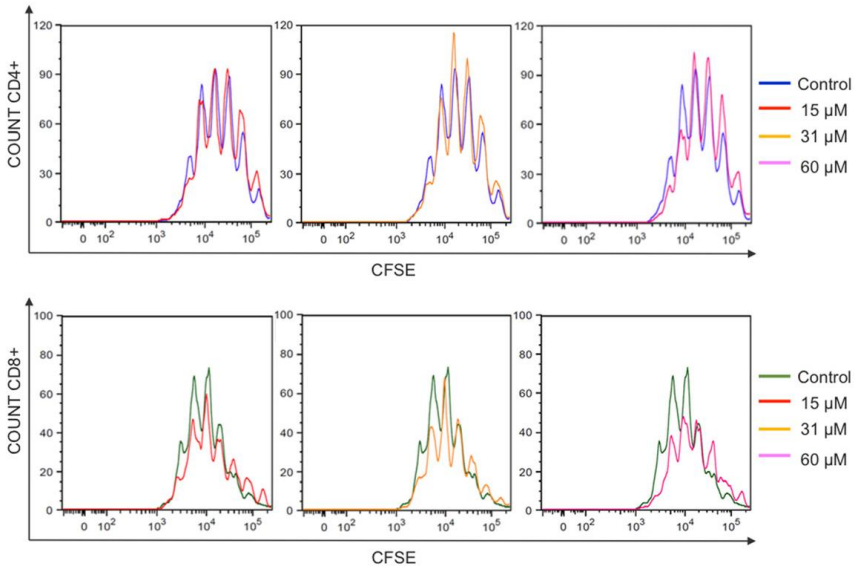


Cytotoxicity is a linear function of concentration: 0.30 × C + 10.3, R^2 = 0.984, across the full 125-fold range. The linear concentration-response suggests mass-action narcosis-mediated toxicity; in the mass-action section of this presentation, we support this interpretation with multiple independent lines of evidence. At the lowest nominal concentration tested (~2 µM), there was still ~9% cytotoxicity, so this assay never demonstrates a non-toxic concentration within the tested range. Normally, one looks for a low-concentration plateau where treated cells are indistinguishable from vehicle control; no such plateau is evident here. Instead, the response remains approximately linear down to the lowest concentration tested, making the ~9% signal unlikely to represent an isolated noisy point. We subsequently questioned whether the nominal concentrations reflected actual drug exposure because ABX464 had been centrifuged out of solution during assay preparation, as the next slide shows.

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Campos excluded dead cells from its flow-cytometry proliferation readout — making the assay incapable of showing that ABX464 does not kill cells. The complementary MTS assay can't distinguish cell death from metabolic suppression. Together, the two assays cannot support ABVX's claim that ABX464 is both non-toxic and has "no effect on cell proliferation."

Campos et al. 2015, Figure 1d. CFSE profiles of viable CD4+ (top row) and CD8+ (bottom row) T cells after 3 days of culture, each panel carrying the untreated control against one concentration of ABX464.



Methods: Purified CD4 and CD8 T cells were labeled with CFSE (carboxyfluorescein succinimidyl ester), cultured for 3 days with ABX464 and analyzed by flow cytometry. CFSE couples covalently to cytoplasmic proteins and its fluorescence approximately halves with each cell division, producing successive division peaks. Campos states that "cellular debris and dead cells were excluded by their light-scattering characteristics." Each panel compares control with a single ABX464 concentration, making direct dose-to-dose comparison difficult. We digitized and replot the profiles on the next slide.

Problems with the assay

Dead cells are excluded from the proliferation readout. Campos states that "cellular debris and dead cells were excluded by their light-scattering characteristics." The histogram therefore describes division only among cells remaining inside the analysis gate.

The assay cannot establish absence of cell killing. If ABX464 preferentially kills proliferating cells, those lost cells disappear before the CFSE histogram is analyzed.

CFSE measures division history among the cells that remain. A loss of highly proliferative cells and a generalized slowing of cell division can both shift the distribution toward fewer completed divisions; without viability and cell-count controls, the assay cannot distinguish them.

Critical controls needed to interpret the result are not reported: no viability dye, cell count per condition, events acquired, donor n, replicates or statistical analysis.

The complementary MTS assay does not solve the problem. MTS measures metabolic activity, not cell number, so reduced MTS signal can reflect cell death, metabolic suppression or both. Thus, neither assay independently establishes the claimed absence of cytotoxicity or impaired proliferation.

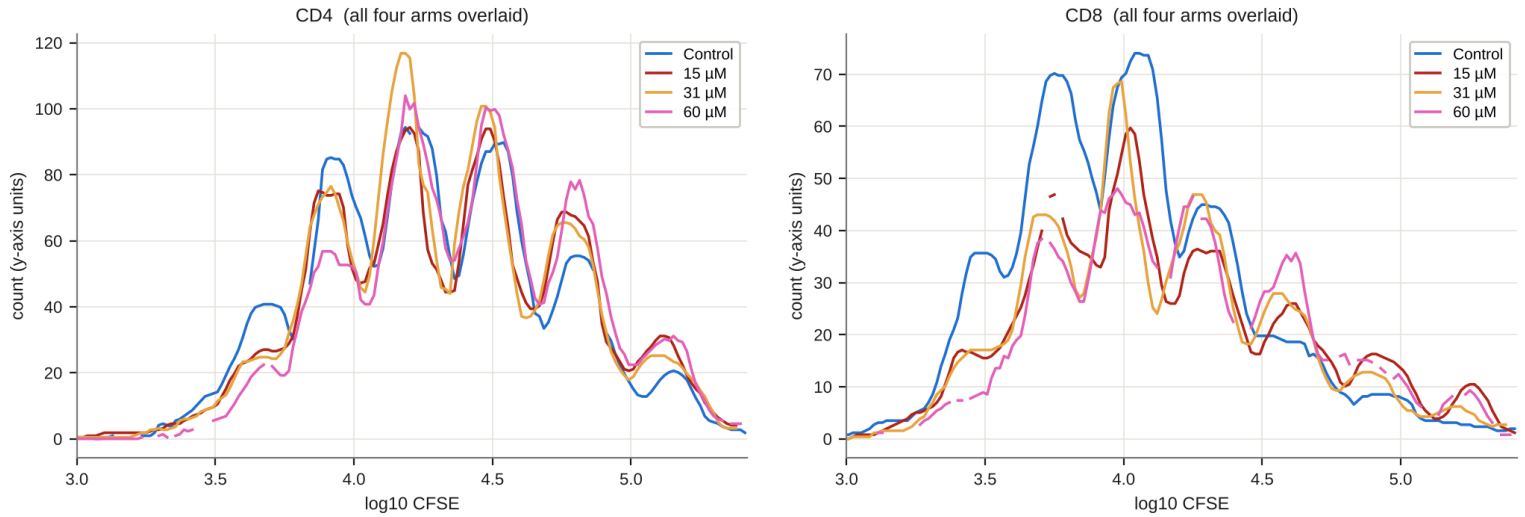
Assay control	Reported in Figure 1d
Viability dye	Not reported
Exclusion applied	Light scatter only
Cell count per condition	Not reported
Events acquired per sample	Not reported
Donors (n)	Not stated
Mitogen or cytokine stimulus	Not stated
CFSE labeling concentration	Not stated
Statistics	Not reported

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our reconstruction directly contradicts Campos's "no effect on cell proliferation" claim -- every ABX464-treated T-cell arm shifts toward fewer completed divisions, even after dead cells were excluded from the analysis. The largest deficit occurs at the highest dose in both CD4 and CD8 cells, consistent with cytotoxicity, slowed proliferation or both.

We digitized and overlaid the CFSE histograms from Campos Fig. 1d. Each peak represents approximately one cell division; a rightward shift therefore indicates fewer completed divisions. Every treated arm shifts relative to control in both CD4 and CD8 cells, with the largest deficit at 60 µM. Importantly, Campos excluded dead cells before generating these histograms. The observed shift therefore occurs among the cells that remained in the analysis and cannot capture cells lost to cytotoxicity. Thus, the figure does not support the claimed null effect: ABX464-treated cells complete fewer divisions, while any treatment-related cell death is excluded from the readout.

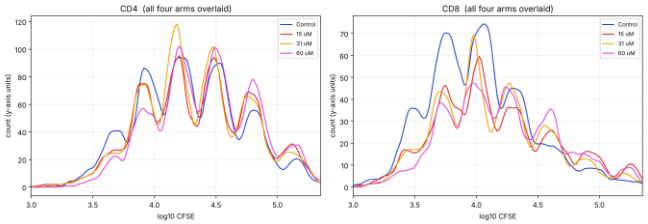
Reconstructed CFSE overlays – Even after dead cells are excluded, ABX464-treated T cells complete fewer divisions than control



Methods: Campos Figure 1d was extracted from the published PDF as its native raster at 300 pixels per inch, without rescaling. Each panel carries the control and one dose, therefore the three panels per lineage were registered on a common axis using the printed decade ticks (10^3, 10^4, 10^5) to convert pixel position to log10 CFSE fluorescence. The four traces were separated by color-channel dominance rather than by nearest-color matching. The control trace is drawn once per panel and is occluded at different points in each. The three copies were merged at each x position to recover the full curve overlay shown. Curve height was read in y-axis count units at every x position. Peaks were located by prominence (scipy.signal.find_peaks, prominence 4 count units, minimum separation 4 pixels). Mean log10 CFSE, division shift, curve area and the division-band fractions were computed from the recovered traces. Across 31 peak-to-peak intervals the mean spacing was 0.296 log10 units (SD 0.039) against log10(2) = 0.301 for a halving, a factor of 1.98. Each peak represents approximately one division generation, allowing the treatment-induced shift in completed divisions to be quantified from the recovered traces..

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Digitizing Campos's own proliferation figure turns its claimed "no effect" into a measurable loss of T-cell progeny -- every treated arm produces fewer progeny than control, reaching a 24% deficit in CD4 and 35% in CD8 at 60 µM. The largest deficits occur at the highest dose and coincide with the strongest cytotoxicity signal in Campos's separate MTS assay.



Campos concludes that ABX464 has "no effect on cell proliferation," but the published CFSE profiles show the opposite direction in every treated comparison. Our reconstruction converts those shifts into completed divisions and progeny per founder cell: all six treated arms produce fewer progeny than their respective controls, with the largest deficits at 60 µM

Importantly, these numbers are calculated only among cells remaining inside Campos's light-scatter gate, which excluded dead cells. The assay therefore cannot determine whether the deficit reflects slower division, preferential loss of proliferating cells, or both — but it clearly does not support a null effect. At the same nominal concentrations, the separate MTS assay also shows progressively greater signal loss, linking the proliferation deficit to the same concentration range in which Campos reports cytotoxicity.

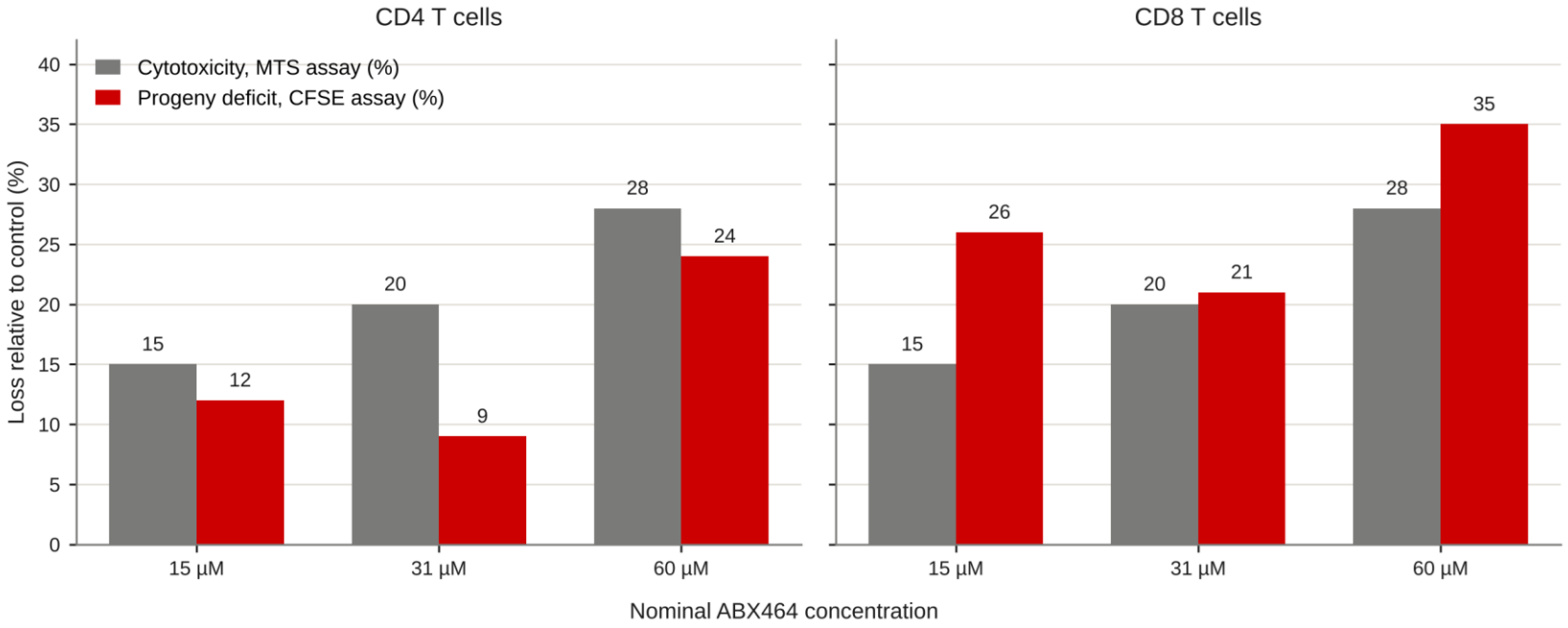
Cell type	Arm (cytotoxicity %)	Progeny per founder cell (% fewer progeny)[1]	Leftmost peak (log10 CFSE)	Shift vs control (divisions)[2]	Most divided (% of curve area below $10^{3.75}$)	Least divided (% of curve area above $10^{4.6}$)	Curve area (% of control arm)
CD4	Control	0 (reference)	3.70	0 (reference)	10.8	22.8	100
CD4	15 µM (15%)	**12%**	3.89	**+0.18**	8.3	28.7	97
CD4	31 µM (20%)	**9%**	3.92	**+0.14**	7.4	26.4	100
CD4	60 µM (28%)	**24%**	3.90	**+0.40**	5.0	31.3	97
CD8	Control	0 (reference)	3.48	0 (reference)	27.3	8.9	100
CD8	15 µM (15%)	**26%**	3.75	**+0.44**	21.1	18.7	77
CD8	31 µM (20%)	**21%**	3.70	**+0.34**	21.7	14.6	77
CD8	60 µM (28%)	**35%**	3.70	**+0.62**	16.5	19.9	74

[1] Progeny per founder cell is 2 raised to the negative division shift, expressed against the control arm. A shift of 0.40 divisions means one starting cell yields 76 progeny for every 100 the control yields, which is the 24% deficit shown.
[2] One division halves CFSE fluorescence, which is 0.301 log10 units. The shift is the difference in mean log10 CFSE between the arm and its control, divided by 0.301.
[3] The comparison holds among cells inside the light-scatter gate. These data cannot distinguish death of the most actively proliferating T cells from a decrease in division rate across all cells.
[4] The figure shows no undivided parent peak, therefore only the difference between arms is measurable, not the absolute number of divisions completed, and no rate can be derived.
[5] No donor count, replicates, event counts or statistics are reported for this panel, therefore no significance test is possible. The direction is the same in 6 of 6 comparisons, which gives a sign-test p value of 0.03 for the direction.
[6] Digitized from the published raster at its native 300 pixels per inch, with the axis calibrated on the printed decade ticks. Across 31 peak-to-peak intervals the mean spacing is 0.296 log10 units (SD 0.039) against log10(2) = 0.301, a factor of 1.98, therefore each peak is one division generation. Peak positions carry about 0.02 log10 units of uncertainty, which is 0.07 of a division.

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Campos's own assays show adverse cellular effects far below its claimed 60 µM toxicity threshold -- at 15 µM, the MTS curve already implies ~15% cytotoxicity while T-cell progeny falls 12% in CD4 and 26% in CD8. Across both lineages, rising cytotoxicity tracks lost progeny.

MTS cytotoxicity and T-cell progeny loss occur together at the same ABX464 concentrations — beginning at 15 µM



The magnitudes agree across two assays run in different cells over different durations.[1] Each percentage point of MTS cytotoxicity[2] corresponds to 0.90 percentage points of lost progeny[3], r = 0.79 across both lineages.[4] Cell death, metabolic suppression with slowed division, and a mixture of the two produce the same result in both assays, because neither assay carries a cell count or a viability dye. The data establish that ABX464 affects the cells at 15 µM and do not identify which process accounts for it. The correlation indicates an effect on either cytotoxicity or proliferation at the same concentrations but does not distinguish which, and it could be both, but it is not null. At 60 µM the deficit is 24% in CD4 and 35% in CD8, within the range of concentrations Tazi's group claims are safe.

1. MTS was run in peripheral blood mononuclear cells (PBMC) over 6 days. CFSE was run in purified CD4 and CD8 T cells over 3 days. MTS was run once in PBMC rather than once per lineage, therefore the same cytotoxicity values appear in both panels.
2. MTS values are interpolated off the Campos Figure 1c regression (cytotoxicity % = 0.30 × C + 10.3, R^2 0.99) at the nominal concentrations used in Figure 1d.
3. Progeny deficit is the shortfall in progeny per founder cell against the control arm, computed as 100 minus 100 times 2 raised to the negative division shift.
4. The 31 µM arm falls below the 15 µM arm in both lineages, which weakens the rank correlation while leaving the slope near one.

Sources: Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Campos created the apparent “safe-dose” range by centrifuging precipitated ABX464 out of the assay stock -- then reporting nominal concentrations as though the discarded drug were still present. The result is an artificially-inflated safety threshold: the published concentrations systematically overstate actual cellular exposure. We measured the actual concentrations of ABX464 by LC-MS/MS (liquid chromatography tandem mass spectrometry).

1. Campos’s own admission

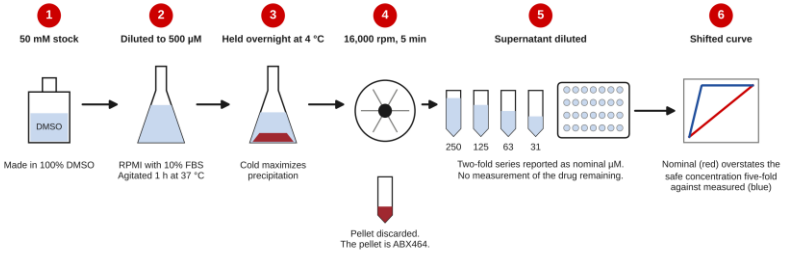
From Campos 2015 results: *“ABX464 is hydrophobic and forms aggregates when applied directly to cell cultures, which leads to some toxicity to the cells (data not shown). To avoid this problem, we prepared a soluble fraction after adding the molecule to cell culture media and elimination of aggregates by centrifugation” (see Methods). Campos also states, “The binding of ABX464 to bovine serum albumin (BSA) retains the molecule in the soluble fraction as determined by mass spectrometry.”*

2. Interpretation -- centrifugation physically removes drug, so nominal concentrations cannot establish the concentrations actually delivered to the cells.

Campos does not report whether its mass-spectrometry assessment was qualitative or quantitative, and no measured concentration is provided. Because the preparation deliberately centrifuges out precipitated ABX464 before the supernatant is diluted into assay wells, the nominal concentrations cannot establish the drug concentrations actually delivered to the cells. We therefore reproduced the preparation and quantified actual exposure by LC-MS/MS.

3. Campos methods/protocol

From Methods: *“A 50 mM stock solution of each tested compound was made in 100% DMSO and stored between −20°C and +4°C. An intermediate solution at 500 µM was prepared in cell culture medium (RPMI) complemented with 10% fetal bovine serum. This solution was agitated for one hour at 37°C on a Thermomixer at 1000 rotations per minute and then stored over-night at +4°C. The following day, the solution was subjected to centrifugation (16,000 rpm) for 5 minutes and the supernatant was used to prepare the various dilutions in cell culture media…”*



4. Why this matters

A 500 µM stock in RPMI with 10% fetal bovine serum is 3,100-fold above the estimated intrinsic solubility of ABX464 of 0.16 µM, calculated from the measured logP of 6.35 and the Form 1 melting point of 120.5 °C ± 2 °C (disclosed in Abivax formulation patent WO2021152129A1). Drug above that intrinsic-solubility limit is prone to precipitate.

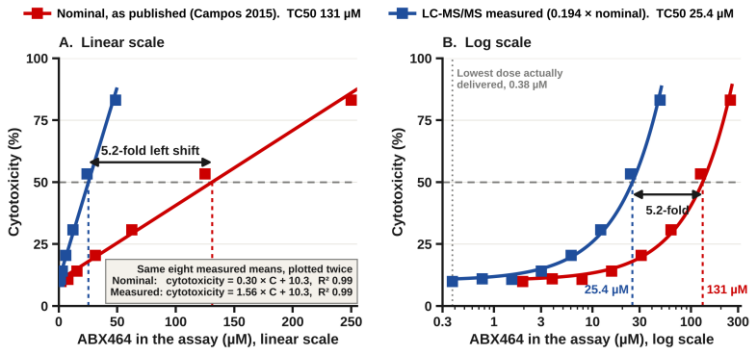
Serum protein buffers the precipitation. Abivax reported no measurement of the drug remaining. We reproduced the preparation cell-free, including the overnight cold incubation and the centrifugation, and measured the drug at each step and in the assay wells by LC-MS/MS.

Sources: Campos et al. 2015; Abivax WO2021152129A1; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our LC-MS/MS finds only ~19% of nominal ABX464 reached the assay wells -- inflating the published safe concentration ~5× and moving the TC50 from 131 µM to ~25 µM. We recovered 85% of the added drug in the pellet, directly locating the missing exposure at the centrifugation step. Corrected for actual exposure, the purported safety margin disappears: biologically meaningful concentrations sit squarely inside the cytotoxic range.

Tazi's group calls 60 µM a safe dose. Delivering 60 µM to the well requires 309 µM nominal, where their regression gives 103% cytotoxicity. The highest tested dose, 250 µM nominal, delivered 48.5 µM actual and produced an 85% cytotoxicity signal. The concentration they describe as non-toxic is projected past 100% when the actual LC-MS/MS-measured concentrations were used.

Our LC-MS/MS measured concentrations (blue) are plotted next to those presented in Campos 2015 for the MTS cytotoxicity assay. Only 19.4% of the nominal drug was present in the assay wells. The table gives the actual against nominal concentrations and the fold elevation over the 0.16 µM intrinsic solubility of ABX464.



Nominal (µM)[1]	Measured (µM)	Recovery (% of nominal)	Actual, fold above solubility (÷ 0.16 µM)[2]	Cytotoxicity, Campos (%)[3]
100	19.5	19.5%	122×	40
50	9.6	19.2%	60×	25
25	4.9	19.4%	30×	18
10	1.9	19.4%	12×	13
5	0.97	19.4%	6.1×	12
1	0.35	35%	2.2×	11
0.5	0.26	51%	1.6×	10
131[4]	***25.4***	***19.4%***	***159×***	***50***
309[4]	***60.0***	***19.4%***	***375×***	***103***

Actual (blue) and nominal (red) concentrations of ABX464 from Campos Figure 1c on a linear (A) and log scale (B) demonstrate that the centrifugation step inflated the safe concentration 5-fold. Both curves intersect at 10% cytotoxicity for the lowest concentration. These data show that a 0.38 µM concentration produces a 10% cytotoxicity signal, and every concentration shifted roughly 5-fold on our LC-MS/MS measurement, which shows that most of the drug was discarded with the pellet. Our mass balance recovered 637 nmol of the 750 nmol added (85%) in the pellet and DMSO wash, and 113 nmol (15%) in the supernatant.[5] Delivering the 60 µM Tazi's group calls safe requires 309 µM nominal, where the regression runs past 100%, meaning the assay has nothing left to measure at that concentration.

1. Campos dosed 1.95 to 250 µM nominal. The 0.5 and 1 µM rows are extrapolated below that range and the 309 µM row above it.
2. Intrinsic solubility of 0.16 µM is estimated by the general solubility equation from the measured logP of 6.35 and the 120.5 °C ± 2 °C melting point of crystal form 1.
3. Cytotoxicity is read off the regression through the eight means in Campos Figure 1c, cytotoxicity % = 0.30 × C + 10.3 with C in nominal µM, R^2 0.99.
4. These two rows are projections off the regression rather than measured concentrations. 131 µM nominal is the TC50. 309 µM nominal places 60 µM in the well.
5. The drug was 1.8% of the 12 mg pellet by weight. The remainder was co-precipitated serum protein and trapped media components.

Sources: Campos et al. 2015; Abivax WO2021152129A1; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Shanley 2022, an independent laboratory studying anthelmintics, assayed ABX464 for cytotoxicity. Their HepG2 data show pronounced mitochondrial toxicity before overt cell loss -- at 100 µM, ~64% of cells remain in glucose while only ~4% of the mitochondrial-dependent signal remains in galactose. Yet Shanley et al. describe ABX464 as "non-mitotoxic" despite reporting a finite MC50 of 81.1 µM - their own data show substantial mitochondrial toxicity within the concentration range they characterize as non-toxic.

Methods: Shanley et al. 2022 tested MMV1581032 (ABX464), a hit from the "Medicines for Malaria Venture Pandemic Response Box", on HepG2 human hepatoma cells (48 h) by crystal violet staining. Two paired arms ran: the cytotoxicity arm with DMEM containing 25 mM glucose and the mitotoxicity arm, where galactose was substituted for glucose (seven concentrations, 2-fold from 100 µM to 1.56 µM, in 10% fetal bovine serum with 0.25% DMSO).

The two assays conducted in tandem:

Replacing glucose with galactose forces cells into oxidative phosphorylation (OXPHOS) for ATP production, because galactose metabolism yields no net ATP. The cell mitochondria cycle hard to fill the ATP deficit. A compound that spares cells on glucose and kills them on galactose is a mitochondrial toxicant.

The signal: With glucose, cytotoxicity was below 50%, with 36% cytotoxicity at 100 µM nominal. With galactose, mitotoxicity was half-maximal at nominal 81.1 µM and 96% at 100 µM. Therefore, mitochondria fail before cells die, as expected for a mass action membrane toxicant.

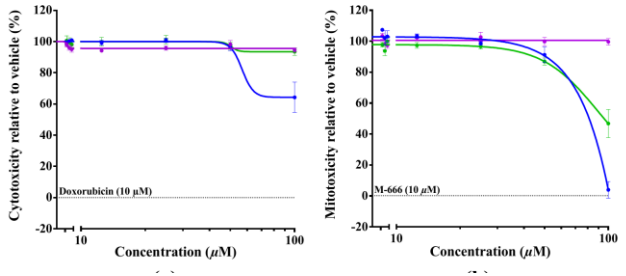
A neutral molecule with logP 6.35 partitions into the inner mitochondrial membrane, the most lipid-dense membrane in the cell, and disrupts the proton gradient that generates ATP.

MTS reduction depends on cellular NAD(P)H and dehydrogenase activity, which both decline when oxidative phosphorylation fails due to mitochondrial failure. For this reason, the 28% signal loss in the MTS assay is consistent with the metabolic collapse observed in PBMC.

Shanley did not measure actual concentrations in the assay wells, therefore we cannot attach a metric to the human liver cell mitotoxicity, since all concentrations tested were above the limit of solubility.

Shanley et al. 2022 describe the same curves as "neither cytotoxic (CC50 ≥ 100 µM) nor mitotoxic (MC50 = 81.1 µM) against HepG2 human hepatoma cells."[4] However, their own data show substantial mitochondrial toxicity within the concentration range they characterize as non-toxic.

Assay item	ABX464
Cytotoxicity, glucose arm (CC50)	≥ 100 µM
Mitotoxicity, galactose arm (MC50)	81.1 µM
Cells remaining at 100 µM, glucose[1]	64%
Signal remaining at 100 µM, galactose[1]	4%
Concentrations tested, nominal	1.56 to 100 µM
Concentrations shown in figure[2]	10 to 100 µM
Centrifugation step	None
Zero on the y axis[3]	Positive control



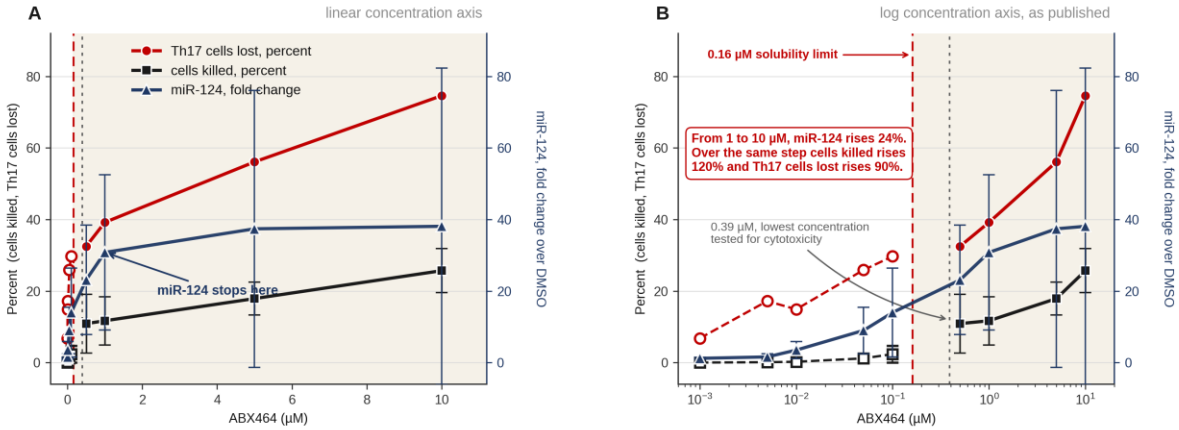
Shanley Figure 4. Left, glucose. Right, galactose. Blue is ABX464 (MMV1581032).

1. The 64% and 96% values were read off the published figure at 300 pixels per inch.
2. The three concentrations nearest the solubility limit (1.56, 3.13 and 6.25 µM) are compressed into the left margin below the labeled decade.
3. Curves were baseline-corrected to a positive control (doxorubicin or M-666, 10 µM), therefore zero on the y axis is that control's maximal effect, not zero cells.
4. Figure 4 legend: "Data points represent one experiment conducted in triplicate; mean ± SEM."

Sources: Shanley et al. 2022; Kamalian et al. 2015; Campos et al. 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's MOA claims, based on correlation, that miR-124 drives Th17 cells down -- yet cytotoxicity, insolubility and mass-action narcosis occur in the same concentration range, providing an obvious alternate explanation for the "efficacy" signal. From 1 to 10 µM, miR-124 rises only ~24% while the cytotoxicity signal rises ~120% and Th17 loss rises ~90%. Thus, the purported miR-124/Th17 "signal" could simply be cytotoxicity in disguise.

Th17 and miR-124 (Apolit 2023) paired with cytotoxicity (Campos 2015). The increases Abivax claims occur at concentrations where the drug is insoluble and cytotoxic in the MTS assay.



Concentration axis: The cytotoxicity series is plotted at the concentrations we measured by LC-MS/MS, which are 19.4% of nominal. The Th17/miR-124 series are plotted at the nominal concentrations Apolit states.

Abivax claims miR-124 lowers the number of Th17 cells. The assays were conducted at concentrations where cytotoxicity rises and the drug is insoluble. From 1 to 10 µM miR-124 rises 24%, while over the same step the MTS cytotoxicity signal rises 120% and Th17 cells lost rises 90%. Cytotoxicity was measurable at each of the eight concentrations Campos tested, down to 0.39 µM.

The reported miR-124 value is a ratio, miR-124 normalized to a reference miRNA, expressed against the same quantity in DMSO. miR-124 is silenced in PBMC, therefore the numerator is signal at or near the detection limit, and no limit of detection is disclosed. If the reference miRNAs decline with cell loss or metabolic suppression, the denominator shrinks and the normalized ratio can rise artifactually. The rise tracks cytotoxicity, making cytotoxicity and denominator instability plausible alternative explanations for the apparent miR-124 signal.

The variance widens for the same reason, since a fixed measurement error in a shrinking denominator becomes a larger error in the ratio. Absolute copies per cell, total RNA yield per well, and raw reference counts at each concentration are not reported, therefore our assessment is inferred. No concurrent viability measure or cell count was disclosed, only that concentrations were held below a stated ceiling "to avoid a cytotoxic effect".

Sources: Campos et al. 2015; Apolit et al. 2023; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Chapter 13. Obefazimod exhibits the disturbing profile of a broad-spectrum anthelmintic/nematocide

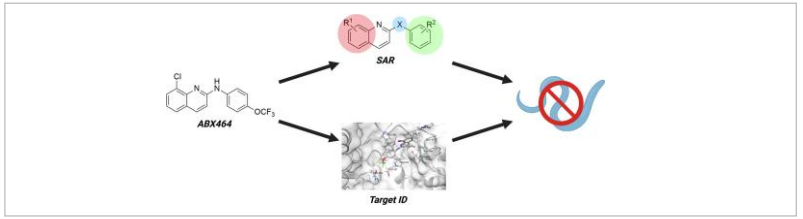
Obefazimod is a broad spectrum nematocide (Shanley et al 2023/24) and mass-action anthelmintic - a class of anti-parasitics that kill worms - with a quinoline scaffold similar to dewormers, fungicides, and agrochemicals

As part of their anthelmintic discovery program, independent Australian researchers evaluated ABX464 (obefazimod) and its analogues against a panel of parasitic nematodes “with a vision of developing a new nematocide.” The group published multiple papers indicating the compound’s activity against parasitic worms ike C. elegans, H. contortus, and others.

Shanley et al 2023 and 2024, respectively: ABX464 pharmacophore as a “new nematocide” with activity against C. elegans, H. contortus, and other parasitic nematodes

Structure activity relationship and target prediction for ABX464 analogues in *Caenorhabditis elegans*

To contribute to the discovery of new anthelmintic entities, we recently evaluated a quinoline derivative (ABX464, called obefazimod; Abivax, France, Fig. 1) (Campos et al., 2015; Vautrin et al., 2019; Tazi et al., 2020; Vermeire et al., 2022) identified in a phenotypic screen of the Pandemic Response Box (curated by the Medicines for Malaria Venture, Switzerland; cf. Shanley et al., 2022; Nick et al., 2022), for its nematocidal activity on *C. elegans* and *H. contortus*. Recently, ABX464 successfully underwent phase II clinical trials in



Structure-activity relationship and target investigation of 2-aryl quinolines with nematocidal activity

Within the context of our anthelmintic discovery program, we recently identified and evaluated a quinoline derivative, called ABX464 or obefazimod, as a nematocidal candidate; synthesised a series of analogues which were assessed for activity against the free-living nematode *Caenorhabditis elegans*; and predicted compound-target relationships by thermal proteome profiling (TPP) and *in silico* docking. Here, we logically extended this work and critically evaluated the anthelmintic activity of ABX464 analogues on *Haemonchus contortus* (barber's pole worm) – a highly pathogenic nematode of ruminant livestock. First, we tested

Highlights

- ABX464, a quinoline molecule, displays anthelmintic activity against *H. contortus*.
- ABX464 and one particular analogue, 36, are also active against several parasitic nematodes.

Source: https://www.sciencedirect.com/science/article/pii/S0968089623003887; https://pmc.ncbi.nlm.nih.gov/articles/PMC10845918/#appsec1

Obefazimod's nematode-killing potency comes from hitting at least 8 unrelated proteins: a textbook mass-action, off-target, promiscuous mechanism -- not a targeted drug -- as predicted by its extreme lipophilicity

Using thermal proteome profiling (TPP) on C. elegans, the Australian researchers identified eight different protein targets that showed altered stability in the presence of ABX464: LUC-7L3, CDO-1, F30F8.9, CRN-3, RAGA-1, NKCC-1, VPS-28, and DAB-1 – a sharp contrast to Abivax's claims that obefazimod selectively modulates miR-124 via CBC binding. These proteins span completely unrelated biological functions - RNA processing, amino acid metabolism, GTPase signaling, ion transport, vesicular sorting, apoptotic DNA fragmentation. The paper shows obefazimod is promiscuous - it binds to multiple unrelated protein targets across diverse biological pathways, consistent with the literature showing that compounds >LogP ~3 exhibit escalating off-target promiscuity.

Shanley et al 2023 and 2024, respectively: ABX464 pharmacophore as a "new nematocide" with activity against C. elegans, H. contortus, and other parasitic nematodes

Structure activity relationship and target prediction for ABX464 analogues in *Caenorhabditis elegans*

2.4. Evidence of multiple ABX464 protein targets in *C. elegans*

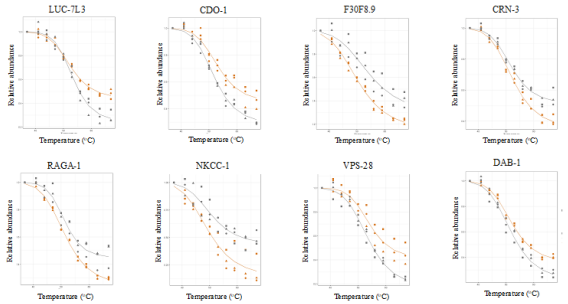
Given the identification of the cap-binding complex (CBC) as a target of ABX464 in humans,[46, 48, 49] it was hypothesised that this might also be a conserved target in nematodes. In a preliminary target identification investigation, a protein lysate of *C. elegans* (L4) was incubated with 50 µM of ABX464 and then subjected to thermal proteome profiling across a gradient of 37 °C to 67 °C,[41] to identify proteins with altered stability in the presence of ABX464.

Structure-activity relationship and target investigation of 2-aryl quinolines with nematocidal activity

3.4. Evidence of multiple ABX464 protein targets in H. contortus

To investigate possible protein targets of ABX464 in *H. contortus*, a protein lysate of xL3s of this species was incubated with 50 µM of ABX464 and then subjected to TPP across a gradient of 37 °C–67 °C (Taki et al., 2022; Shanley et al., 2024), to identify proteins with altered stability in the presence of ABX464.

Multiple ABX464 protein targets in C. elegans (Shanley, 2023 – supplementary figure 3)



Supplementary Figure 3. The thermal shift plots demonstrating the melting curves of eight protein targets (LUC-7L3, CDO-1, F30F8.9, CRN-3, RAGA-1, NKCC-1, VPS-28 and DAB-1) for ABX464 (grey) compared to a PBS control (orange). Data taken from three replicates, at 10 distinct temperatures (37, 41, 44, 47, 50, 53, 56, 59, 63 and 67 °C).

Source: https://www.sciencedirect.com/science/article/pii/S0968089623003887; https://pmc.ncbi.nlm.nih.gov/articles/PMC10845918/#appsec1

Obefazimod's nematocidal activity was discovered during high throughput screens on 400 compounds in a Pandemic Response Box – as ABVX was pumping its stock as a COVID play during the pandemic's peak in May 2020

A non-profit called Medicines for Malaria Venture included ABX-464 in a pandemic response box with 400 compounds – 201 antibacterials, 153 antivirals, and 46 antifungals – to provide researchers with a set of candidates for screening against infective diseases. ABX-464 was identified as one of the compounds with "consistent and repeatable nematocidal activity."

ABVX press releasees on ABX-464 inhibition of COVID virus, May/Dec 2020

The Pandemic Response Box–Accelerating Drug Discovery Efforts after Disease Outbreaks



Structure activity relationship and target prediction for ABX464 analogues in *Caenorhabditis elegans*

Recent work[42, 43] has led to the discovery of a number of novel compounds whose potencies have not yet been optimised and whose targets in nematodes are unknown. For instance, in high throughput screens,[45, 46] we identified a number of compounds (including HF-00014 and ABX464) with consistent and repeatable nematocidal activity in *C. elegans*. ABX464 – a quinoline derivative (Fig. 1) – originates from the *Pandemic Response Box*, established and curated by the Medicines for Malaria Venture (MMV; Geneva, Switzerland). Of the 400

ABVX press releasees on ABX-464 inhibition of COVID virus, May/Dec 2020

ABX464 INHIBITS REPLICATION OF SARS-CoV-2 (COVID-19) IN RECONSTITUTED HUMAN RESPIRATORY EPITHELIUM MODEL

May 14, 2020 PDF Version

ABX464 IS THE ONLY DRUG CANDIDATE WITH A POTENTIAL TRIPLE ACTION FOR COVID-19 TREATMENT: ANTIVIRAL, ANTI-INFLAMMATORY AND TISSUE REPAIR

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ABIVAX'S COVID-19 PHASE 2B/3 MIR-AGE TRIAL WITH ABX464 DECLARED RESEARCH NATIONAL PRIORITY BY THE FRENCH GOVERNMENT'S CLINICAL TRIAL COUNCIL

Source: https://pubmed.ncbi.nlm.nih.gov/35286809/; https://dndi.org/wp-content/uploads/2019/06/PandemicResponseBox_FactSheet.pdf; https://ir.abivax.com/news-releases/news-release-details/abx464-inhibits-replication-sars-cov-2-covid-19-reconstituted

Obefazimod anthelmintic activity: predicted to target AKR proteins as well – a critical class in humans -- “disrupts one or more key biological functions, leading to immobilization and death of the parasite”

Using thermal proteome profiling (TPP) on a second nematode, H. contortus, the Australian researchers indicated obefazimod interacting with AKR proteins – “the general function of AKR proteins is to reduce carbonyl substrates, playing an important role across a number of various species...”

Shanley 2024: ABX464 activity against larvae/adult worms via AKR target

Structure-activity relationship and target investigation of 2-aryl quinolines with nematocidal activity

proteins. Although the complete function of HCON_00074590 has not been annotated, the general function of the AKR proteins is to reduce carbonyl substrates, playing an important role across a number of various species (reviewed by Penning, 2015). In human health, AKRs have been implicated in the pathogenesis of diabetes, bile acid deficiency and in retinoic acid signalling, becoming the focus of several drug development programs (Penning, 2015). It is possible that the interaction of ABX464 and HCON_00074590 disrupts one or more key biological functions, leading to the immobilisation and death of the parasite.

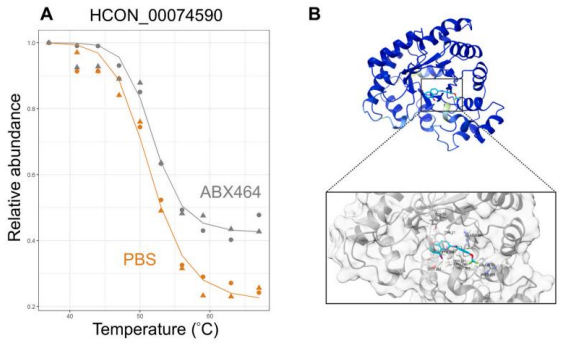
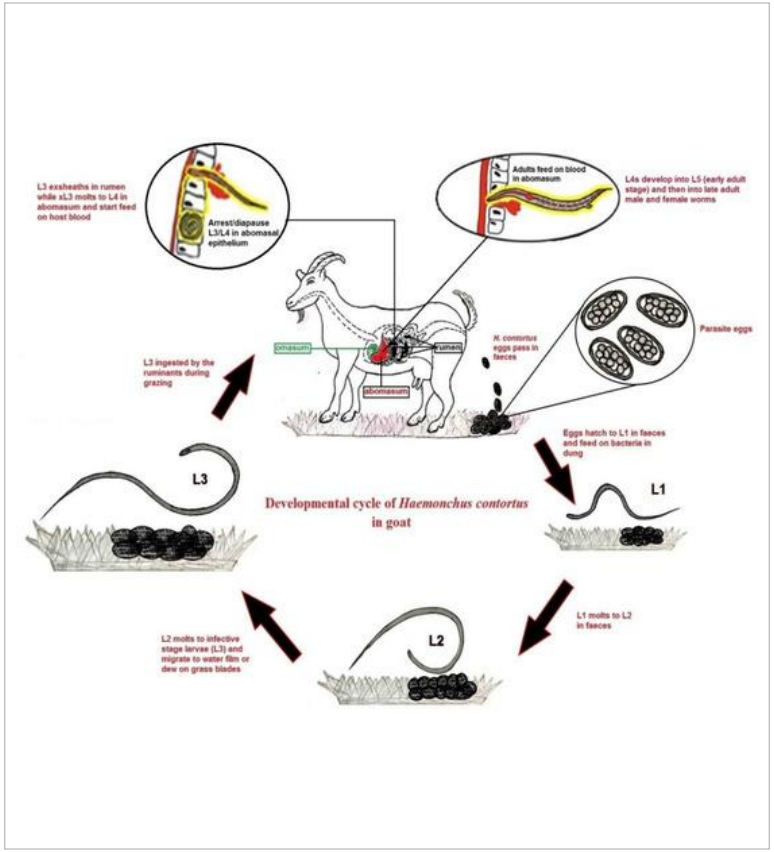


Fig. 2. Thermal proteome profiling and *in silico* docking. (A) Thermal shift plot for the melting curves (temperature gradient 37 °C–67 °C) of a potential *Haemonchus contortus* protein target of ABX464, HCON_00074590. Data from two replicates. (B) The predicted interaction of the three-dimensional structure of HCON_00074590 (predicted using the algorithm Alphafold 2; UniProt accession number: A0A7I5E8V5) with ABX464 using the algorithm AutoDock Vina (displayed using ChimeraX software), with an inset showing the predicted binding pocket and associated residues. Carbon (grey), oxygen (red), nitrogen (blue), fluorine (green), chlorine (purple) and hydrogen (white) atoms are colour-coded.



Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10845918/; https://www.mdpi.com/2076-393X/8/3/555

AKR biology maps onto the malignancies seen in Phase 3 -- linked to NSCLC, breast, prostate, and other cancers – “considered a tumor marker” which can reinforce AHR-driven carcinogenesis

Penning’s authoritative review calls AKR1B10 a tumor marker in NSCLC and ties the AKR1C enzymes to the androgen and estrogen flux behind prostate and breast cancer. Burczynski and Penning showed that AKR-generated quinones activate AHR and redox-cycle into oxidative DNA damage. We are unaware of Abivax characterizing AKR induction in any tissue.

Penning 2015 – seminal, highly-cited AKR review

The aldo-keto reductases (AKRs): Overview

fidarestat [51] . AKR1B10 has been implicated in regulating retinoic signaling by converting all-*trans*-retinaldehyde to retinol [52, 53] and is highly overexpressed in NSCLC [54] and in hepatocarcinogenesis [55] and is considered a tumor marker. Interception of retinoic acid signaling could also prevent the differentiation of cancer stem cells. A sterol based inhibitor oleanolic acid [56] as well as the nonsteroidal anti-inflammatory drug sulindac [57] are lead compounds for inhibitor development for AKR1B10.

Burczynski & Penning 2000 – AKR to AHR pathway initiation

Genotoxic Polycyclic Aromatic Hydrocarbon *ortho*-Quinones Generated by Aldo-Keto Reductases Induce CYP1A1 via Nuclear Translocation of the Aryl Hydrocarbon Receptor[1]

Fukimoto 2005

Overexpression of the aldo-keto reductase family protein AKR1B10 is highly correlated with smokers' non-small cell lung carcinomas

The malignancy pattern is directionally consistent with established AKR cancer biology, and AKR metabolism offers a documented route into AHR-mediated genotoxic stress.

Penning and Byrnes 2009 – figure 2 shows AKR1C3 creating a pro-estrogenic pathway in breast tissue

Steroid hormone transforming aldo-keto reductases and cancer

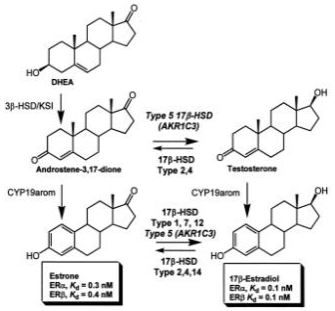


Figure 2.
Role of AKR1C3 in the local production of 17β-estradiol in the breast.

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC4388799/pdf/nihms640041.pdf; https://aacrjournals.org/cancerres/article/60/4/908/507343/Genotoxic-Polycyclic-Aromatic-Hydrocarbon-ortho; https://pubmed.ncbi.nlm.nih.gov/15755999/; https://pubmed.ncbi.nlm.nih.gov/19250190/

Obefazimod kills nematodes via mass action fingerprint of an agrochemical molecule, not a targeted therapeutic – cytotoxic accumulation, hits 8+ unrelated proteins, AKR target, active across various parasite species

In the published anthelmintic discovery program, obefazimod kills nematodes (C. elegans, H. contortus, A. ceylanicum, S. ratti, T. muris) with IC50s of 3.5–7.2 µM -- concentrations achievable in lipid-rich tissues: cytotoxic activity at low-µM IC50s, 9 unrelated protein binding partners (TPP), aldo-keto reductase (AKR) target in H. contortus, broad-spectrum activity across 5 nematode species in 3 evolutionary clades -- the signature of a non-selective lipophilic agrochemical, not a targeted drug.

Classic signature of a mass-action mechanism

1 **Cytotoxic at IC50**
Inhibits nematode motility (3.5–7.2 µM) and larval development (3.5 µM) — kill, not modulation. Adult H. contortus motility reduced 73% at 40 µM.

2 **9 unrelated protein targets**
TPP: 8 C. elegans proteins (splicing, GTP-binding, ion transport, ribosomal, vesicular sorting, neural) + 1 H. contortus AKR. None are the claimed human target.

3 **Aldo-keto reductase (AKR) target**
H. contortus AKR target (HCON_00074590) is a metabolic enzyme — the classic non-selective binding signature of small lipophilic xenobiotics.

4 **Active across 3 evolutionary clades**
Kills worms in clades I, IV, V (H. contortus, C. elegans, A. ceylanicum, N. americanus, He. polygyrus, S. ratti, T. muris). Targeted anthelmintics are species-restricted; mass-action agents are not.

Nematocidal activity across species (Shanley 2024)

Monepantel — a real targeted anthelmintic — is **13–240× more potent than obefazimod** across the same nematode species. A targeted drug works at nanomolar concentrations against its specific receptor; a mass-action agent requires far higher micromolar concentrations and works across phylogenetically distant species. Obefazimod's profile is the latter.

Species / stage	Clade	ABX464 (obefazimod)	Monepantel (targeted ctrl)
C. elegans young adult	V	IC50 7.2 µM	IC50 0.03 µM
H. contortus larvae	V	IC50 6.0 µM	IC50 0.08 µM
H. contortus development	V	IC50 3.5 µM	IC50 0.27 µM
H. contortus adult ♀	V	73% kill @ 40 µM	100% kill
A. ceylanicum (hookworm)	V	43% kill @ 10 µM	—
N. americanus (hookworm)	V	13% kill @ 10 µM	—
He. polygyrus	V	15% kill @ 50 µM	—
S. ratti	IV	64% kill @ 10 µM	—
T. muris adults	I	25% kill @ 10 µM	—

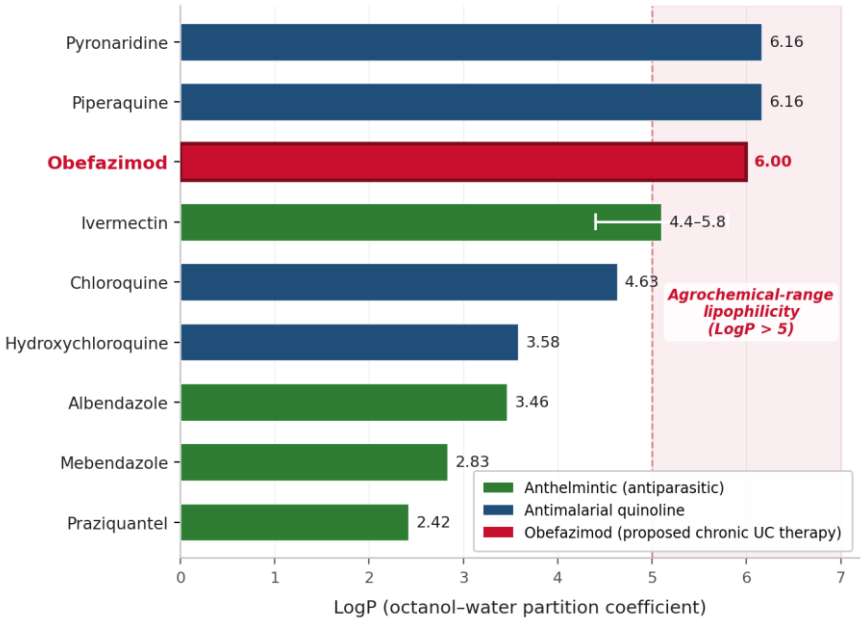
Source: https://www.sciencedirect.com/science/article/pii/S0968089623003887; https://pmc.ncbi.nlm.nih.gov/articles/PMC10845918/#appsec1

Obefazimod out-lipophiles anthelmintics like chloroquine and ivermectin — which are pulse-dosed as chronic exposure is toxic – yet is dosed daily

Anthelmintics have similar or lower logP vs. obefazimod, yet are given as single annual or semiannual doses to kill parasites then clear. Obefazimod takes similar or worse lipophilicity with proven anthelmintic activity -- and proposes indefinite daily dosing for a non-fatal indication.

Anthelmintics as a drug class are **not** dosed chronically. Obefazimod takes a molecule with similar bioactivity and lipophilicity and proposes the opposite — daily, indefinite dosing for a non-fatal disease.

Obefazimod is similar to or more lipophilic than antiparasitic drugs



HOW ANTHELMINTICS ARE DOSED: PULSE THEN CLEAR

Albendazole, ivermectin, and praziquantel are given as a single annual dose in mass drug administration — at most twice a year. Hit the parasite at high transient concentration, then let the drug clear so brief exposure doesn't accumulate to toxic tissue levels.

CHRONIC DOSING DOSe WITH A LIPOPHILIC QUINOLINE

Chloroquine / HCQ — the cautionary parallel. Dosed chronically (unlike anthelmintics), a lipophilic quinoline causes cumulative, duration-dependent toxicity: retinopathy risk **doubles every 5 years** and rises sharply after 1,000 g cumulative; long-term use also drives cardiomyopathy and conduction disorders. Invisible until years 5–7+.

IVERMECTIN PRECEDENT

Ivermectin (J. Med. Chem. 2025): "safe at low nanomolar concentrations, becomes cytotoxic at low micromolar concentrations" via nonspecific membrane-bilayer perturbation — dysregulating GPCRs, ion channels, hERG, FXR. This is the same lipophilic-membrane mechanism implied by obefazimod's 9-protein pharmacology signature in nematodes.

LogP sources: albendazole 3.46 & ivermectin ALogP 4.4–5.8 (Pettarin et al. / membrane-partitioning literature); chloroquine ~4.63, piperaquine & pyronaridine 6.16 (ACD LogP, AAC 2006); obefazimod ~6 (computed). Dosing: WHO/MDA single annual–semiannual regimens. Chloroquine/HCQ toxicity: AAO screening guidance; healio/ACR 2021. Mechanism: Membrane Perturbations by Ivermectin, J. Med. Chem. 2025 (10.1021/acs.jmedchem.5c01610).

Chapter 14. The “miR-124 upregulation” illusion

All six independent expression databases and ABVX's own studies agree that mature miR-124 is not expressed in blood, immune cells and gut – undermining its MOA narrative which requires functional miR-124 in peripheral immune cells

Abivax cites GeneCards through Qin for peripheral expression -- it is not a database using correct miR detection methods that can cleanly distinguish mature miR-124 from its host transcrips . All the other databases report 0.

Source	What it measures	miR-124 in blood, immune cells and gut	Reference
Human miRNA Tissue Atlas	small RNA sequencing across human tissues	one of the highest brain specificity scores of any microRNA; blood at background	Ludwig et al. 2016, Nucleic Acids Res 44:3865
miRNATissueAtlas2	sequencing update of the same atlas	brain restricted, no peripheral expression	Keller et al. 2022, Nucleic Acids Res 50:D211
FANTOM5 CAGE atlas	cap analysis of gene expression, miRNA promoters and mature miRNAs	mature miR-124 detected only in central nervous system derived cells	de Rie et al. 2017, Nat Biotechnol 35:872
miRmine	human miRNA expression profiles from public small RNA sequencing	at or near background in blood	Panwar et al. 2017, Bioinformatics 33:1554
Mouse small RNA tissue atlas	small RNA sequencing across mouse tissues	brain specific, absent from the blood lineage	Isakova et al. 2020, PNAS 117:25634
HeLa, the standard non-neuronal line. Abivax tested it themselves and found no expression	miR-124 qPCR in wild type HeLa and in HeLa transfected with lncRNA 0599-205	HeLa carry no miR-124. ABX464 at 5 µM, no change in WT or transfected cells. Abivax: "we failed to detect an upregulation of miR-124 in transfected HeLa cells in response to ABX464 treatment"	Chebli et al. 2017, Sci Rep 7:4071; Lim et al. 2005, Nature 433:769
Abivax, primary immune cells from Vautrin	microarray and qPCR in lymphoid cells and monocyte derived macrophages	"ABX464 treatment resulted in upregulation of miR-124 in lymphoid cells but not in monocyte derived macrophages, where the expression of miR-124 was undetectable" (Figs 3C and S4B). No Cq value and no detection threshold are stated	Vautrin et al. 2019, Sci Rep 9:792
Abivax, droplet digital PCR their own filing	copy number per cell, 217 patients on 50 mg	whole blood 0.00000 at baseline and 0.00013 at week 48. Rectal 0.00065 and 0.00255	ClinicalTrials.gov NCT04023396
GeneCards, through Qin 2016 the source Abivax cites	gene centric aggregator, microarray probes	reports immune expression. Microarray cannot separate the host transcript MIR124-1HG from the mature 22-mer, so host gene signal reads as miR-124	Qin et al. 2016

miR-124 is not merely low in immune cells, it is switched off. All three loci, MIR124-1, MIR124-2 and MIR124-3, carry CpG islands that are hypermethylated and transcriptionally silenced in non-neuronal cells, including the hematopoietic and immune lineage (Lujambio et al. 2007, Cancer Res 67:1424; Agirre et al. 2009, Cancer Res 69:4443). ABVX's 2019 paper reports it undetectable in macrophages, and their 2023 paper reports fold changes in the same cell type. Their filing reports zero copies per cell in whole blood at baseline and 0.00013 after a year of dosing.

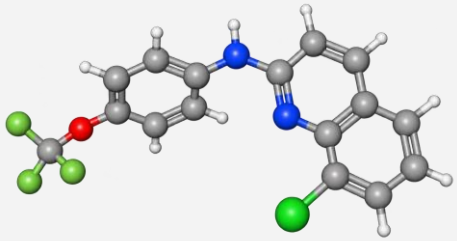
Sources: Ludwig 2016; Keller 2022; de Rie 2017; Panwar 2017; Isakova 2020; Chebli 2017; Lim 2005; Vautrin 2019; NCT04023396; Lujambio 2007; Agirre 2009; Scorpion Capital analysis/literature review

ABX464 (parent) and N-Glu (metabolite) have fundamentally different and opposing properties -- undermining ABVX/Tazi's claims of a shared CBC binding mechanism. Our DLS results flatly invalidate the mechanistic claim.

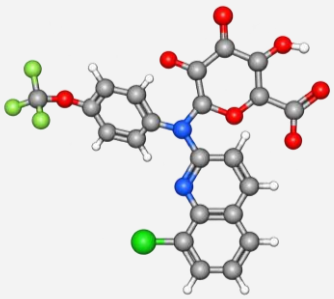
Parent and N-Glu have opposing chemical properties, but the ABVX/Tazi group's claim is that both activate the same binding site on the cap-binding complex (CBC), citing data not shown. Our DLS results invalidate the Tazi group's CBC binding claim. The odds of N-Glu binding the same pocket as ABX464 are low. As we show in a later chapter, third-party Equillium reports no N-Glu activity at the AhR in a 24-hour reporter assay, while ABX464 showed strong activation. In addition, our PK analysis leads us to conclude that N-Glu distributes to total body water and ABX464 to tissues.

	ABX464	N-Glu
Plasma $T_{1/2}$	0.8 hours	4 .2 days
Lipid preference	Lipid loving	Highly hydrophilic
Cell membranes	Passively permeable	Low permeability
Water preference	Water hating	Water loving
Plasma levels	Extremely low*	Extremely high
Cation charge	Neutral	Neutral
Anion charge	Neutral	Negatively charged
Rotation	Freely rotating	Constrained
Shape	Planar	Bulky
Molecular weight	339	515

ABX464



N-Glu



Sources: Campos et al. 2015; Tazi et al. 2021; Vautrin et al. 2019; DrugBank DB14828; miR-124 investor webinar, 27 May 2026; Scorpion Capital DLS and autofluorescence report and lab experiments; Scorpion Capital estimates, analysis, and literature/publication review; chemical structure adapted from Campos et al., Retrovirology (2015), Fig. 1a; 3D molecular visualization using ChatGPT

ABVX has a pattern of carrying miR-124 as an endpoint – and then not posting the results. Phase 2a prespecified miR-124 and IL-22 as endpoints in 2017 and submitted results in 2021. The registry returned the submission to draft 29 days later -- both measures disappeared from the resubmission. The record posted in 2023 had no value for either. Yet Tazi 2021 claims 7.6-fold in biopsy and >200-fold in blood -- without citing a study record or data.

Tazi et al. 2021 states the Phase 2a numbers in text. The paper carries no reference on these three sentences.

"In rectal biopsies of patients treated with ABX464 for 56 days, miR-124 was increased 7.6-fold compared with the placebo group. A larger increase in miR-124 in excess of 200-fold was observed in peripheral blood cells. This ABX464-driven induction of miR-124 was sustained for at least 360 days." **No reference to study record or publication. No time point for blood.**

NCT03093259, ABX464-101, Phase 2a: study start 16 November 2017; primary completion 25 July 2018; overall completion 4 February 2019.

2 endpoints deleted (miR-124 was one) and 2 added (FCP and partial Mayo score), filed in March 2017

Endpoint as filed	Endpoint type	Fate
MicroRNA-124 levels	Secondary	Deleted
IL-22 expression levels	Secondary	Deleted
Treatment-emergent adverse events	Primary	Posted
Clinical Remission (Total Mayo)	Secondary	Posted
Total Mayo Score	Secondary	Posted
Fecal Calprotectin	Not filed	Added at posting
Partial Mayo Score	Not filed	Added at posting

The two biomarker endpoints were deleted together. The clinical endpoints were posted. Two endpoints absent from the 2017 filing appear in the posted version. The time frames were cut from week 4 and week 8 to week 8.

The record of versions submitted and when

- **28 Mar 2017** Version 0 posted. MicroRNA-124 levels filed as a secondary outcome, in whole blood (PAXgene), week 4 and week 8
- **4 Dec 2018** Version 4 posted, status Completed. The prespecified measure text is unchanged across versions 0 to 4
- **4 Feb 2019** Study completion (actual)
- **14 Oct 2021** RELEASE. Abivax S.A. submits results, 983 days after completion
- **12 Nov 2021** RESET. The registry returns the submission to draft, 29 days later
- **9 May 2022** Quality control cleared on a resubmission carrying no miR-124
- **8 Feb 2023** Version 5 posted with no MicroRNA-124

The RELEASE and RESET events are recorded on version 4 under the responsible party Abivax S.A. Versions 0 to 4 carry no results section, so the measure exists as a prespecification with no valued attached.

Abivax wrote miR-124 into the COVID-19 trial and RA protocols, as a secondary endpoint. Neither results posted. ABX464-301 completed and posted results April 2022, and miR-124 appears in none of its twenty secondary endpoints. Across the seven versions of the Phase 2a record, no miR-124 value was retained.

Sources: Tazi et al. 2021; NCT03093259 record history; NCT04393038 record history; NCT03813199 record history; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ClinicalTrials.gov's absolute ddPCR record shows no miR-124: ALL ZEROS -- 0.00000 copies/cell in blood at baseline and ≤0.00255 copies/cell in tissue

The first posting of miR-124 was Phase 2b maintenance: miR-124 dataset posted to Clintrials.gov on April 27, 2025, copy number per cell by ddPCR, all zeros (blood, rectal and sigmoidal biopsy). No revisions. The registry accepted these data and these units, copy number/cell. These are absolute counts, not normalized ratios: even the highest reported value remains far below one molecule per cell.

ClinicalTrials.gov NCT04023396, Phase 2b maintenance -- baseline & week 48; blood, rectal & sigmoidal biopsies

miR-124 expression | ABX464 50 mg, n=217 | unit: copy number/cell		
Whole blood — Baseline	**0.00000**	(SD = 0.00000)
Whole blood — Week 24	**0.00011**	(SD = 0.00015)
Whole blood — Week 48	**0.00013**	(SD = 0.00026)
Rectal biopsy — Baseline	**0.00065**	(SD = 0.00211)
Rectal biopsy — Week 48 **(4-fold ↑)**	**0.00255**	(SD = 0.00252)
Sigmoidal biopsy — Baseline	**0.00035**	(SD = 0.00050)
Sigmoidal biopsy — Week 48 **(6-fold ↑)***	**0.00225**	(SD = 0.00216)

*Abivax reported 6.7-fold change for Phase 2a, wk 8

Scale anchor: biological miR-124 in neurons much higher

Neuron (physiological): **140,000 – 420,000 copies/cell**

Abivax max reported (rectal Wk 48): **0.00255 copies/cell**

Ratio: ~10^8 (physiological expression is 100,000,000× higher)

ddPCR, the gold standard for absolute quantification is all zeros. No ratios just copy per cell

- **Unlike RT-qPCR (miR-16 normalized, log-scale), ddPCR provides an absolute count converted to copy number per cell. For ddPCR, sample is diluted into ~20,000 nanoliter droplets. The positive droplets are counted, and the fraction yields a direct RNA count — no reference gene, standard curve or fold change.**
- **Expression is zero, just as the six miR-124 databases predict.**
- **There is a 4 to 6-fold rise in biopsy samples (48w) vs baseline. It's meaningless biologically, but it is a numerical increase.**
- **Fold-change is the metric Abivax routinely uses for their reporting after normalizing it against housekeeping genes or DNA, and again against baseline which inflates the values thousands to millions of fold.**
- **All values: 0.00000 to 0.00255 copies/cell across blood and biopsy sample. At ~100,000 cells per reaction, the highest value = ~1 droplet in 80 scoring positive. Less than a copy per cell.**
- **Whole-blood baseline (0.00000): no positive droplets detected at all. Dividing zero into any number gives infinity, so to report blood as fold change Abivax had to supply a quantity for zero. That quantity determines the fold change. Set it low enough and the fold change is enormous.**

Prior disclosures (Tazi 2021 in Drug Discov Today, the ECCO 2026 ABTECT poster and the November 2025 ClinicalTrials.gov update) report miR-16-normalized ratios or fold-changes from which absolute abundance cannot be back-calculated. This is the first, and as of October 27, 2026, the only true ddPCR record we found. But on 28 November 2025, a second set of miR-124 numbers posted to Clintrials.gov, blood only, and with numbers inflated thousands to millions of fold compared to those shown here, also labeled ddPCR, Copy number per cell.

Source: ClinicalTrials.gov NCT04023396, Outcome Measure 10 (miR-124 expression) — Desroys du Roure (Abivax Clinical Operations), posted April 27, 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's miR-124 data is preposterous – they claim to detect miR-124 at fractions of an atom per cell. miR-124 is at or below one ten-thousandth of a copy per cell on ClinTrials.gov -- 0.00013 copies of miR-124 per cell = 1 miR-124 molecule per 7,700 cells = ~7% of the mass of a single carbon atom per cell. You cannot have a fraction of a regulatory molecule!

The same clinical program reports blood miR-124 as zero, then 8,517 "copies/cell," then 0.00013 -- these values cannot represent one consistent, credible biological signal or mechanism.

What 0.00013 copies/cell represents - Abivax's highest reported whole-blood ddPCR value, week 48

A SINGLE mature miR-124-3p molecule:

- 20 nucleotides (hsa-miR-124-3p, the functional strand and the one the TaqMan 477879 assay targets)
- Sequence: UAAGGCACGCGGUGAAUGCC
- Molecular weight: ~6,525 g/mol
- 671 atoms total (192 C, 239 H, 81 N, 139 O, 20 P)
- Mass per molecule: 1.08 × 10^{-20} g (= 10.8 zeptograms)

0.00013 copies/cell × molecular constituents:

miR-124 molecules per cell	0.00013	*(1/7,692 of one molecule)*
Nucleotides per cell	0.0026	*(1/385 of one nucleotide)*
All atoms per cell	0.087	*(< 1/11 of a single atom)*
Carbon atoms per cell	0.025	*(2.5% of one C atom)*
Mass per cell	1.41 × 10^{-24} g	*(= 1.41 yoctograms)*
vs. one C atom mass (1.99×10^{-23} g)	0.071	*→ 7.1% of a single carbon atom*

The biologically impossible trajectory - blood miR-124, same programme, same assay, across disclosure venues

Timepoint	What Abivax reports	Source
Day 0 (baseline)	0.00000 copies/cell	*Desroys 2025 ddPCR (raw)*
Week 8 (~2 mo)	8,517 'copies/cell' (50 mg)	*Apolit 2023 / Cataldi (normalized)*
Week 16 (~4 mo)	7,723 'copies/cell' (50 mg)	*Cataldi, registry only (normalized)*
Week 24 (~6 mo)	0.00011 copies/cell	*Desroys 2025 ddPCR (raw)*
Week 48 (~12 mo)	0.00013 copies/cell	*Desroys 2025 ddPCR (raw)*

There is no biological mechanism that produces:

Zero at baseline, 8,517 at month 2 and 7,723 at month 4, then back to 0.00011 and 0.00013 at months 6 and 12, while the patient is still on drug.

A real induction either persists or decays gradually. This trajectory only exists because two different methodologies disagree about what they're measuring.

Both labels say "copies/cell". Only the green readings are raw ddPCR. The red values are miR-16-normalized ratios relabeled as copies per cell. The week 16 pair is on ClinicalTrials.gov and in no publication.

0.00013 miR-124 molecules per cell = about 7% of the mass of a single carbon atom per cell

Regulatory miRNAs function by binding messenger RNAs at hundreds to thousands of copies per cell. The reported values are not low expression. They are non-existence dressed up as a numerical readout. When the same molecule in the same patient at adjacent timepoints reads zero on raw ddPCR but thousands on a miR-16-normalized assay, only one of those is measuring biology.

Sources/notes: NCT04023396, Desroys du Roure, posted 27 April 2025; NCT03760003 outcome measure 16, Cataldi, posted 28 November 2025; Apolit et al. 2023; Scorpion Capital analysis, modeling, estimates, and literature/publication review ; **Avogadro's number 6.022 × 10^{23}; mass of one carbon atom 1.99 × 10^{-23} g; miR-124-3p composition from the mature sequence**

The same Phase 2b numbers are called both “copies/cell” and “miR-124 copies (miR16 normalized)” -- they cannot be both. The ClinicalTrials.gov Phase 2b “ddPCR copies/cell” values are identical to Apolit 2023 published values despite incompatible descriptions of what the numbers measure.

Postings on ClinicalTrials.gov label these values ddPCR, copy number per cell, in three places: the measure title, the unit field and the measure description. They are ratios, not absolute counts per cell. Only blood is posted. The rectal biopsy values appear to have been removed during the QA process..

Blood, week 8	Apolit et al. 2023 (PMC10132720), text body	ClinicalTrials.gov NCT03760003, Outcome 16 (Cataldi, submitted 14 Nov 2025, posted 28 Nov 2025)	Identical
Matching Placebo	28.93	28.93	yes
ABX464 25 mg	4,598	4,598	yes
ABX464 50 mg	8,517	8,517	yes
ABX464 100 mg	13,753	13,753	yes

Both sets of numbers cannot be ddPCR. Apolit describes them as normalized values, using a sample-specific miR-16 factor that the methods state varies per sample and per batch, then normalization to baseline. The methods do not explain the process. We found the draft history on ClinicalTrials.gov had retained the QA draft history (next slide).

One set of numbers with four descriptions -- all in Apolit et al. 2023:

Location of citation	What Abivax call these numbers, quoted verbatim
Results text citing 4e	“the mean number of copies/cell: placebo, 28.93; ABX464 [25, 50, and 100 mg], 4,598, 8,517, and 13,753, respectively”
Figure 4e axis	“miR-124 copies (miR16 normalized)”
Statistics section	“The miR-124 modulation is expressed in fold change”
Methods	“The normalized miR16 copy number was calculated using a sample-specific normalization factor that considers the relative expression of miR-16 per sample per batch”

OMISSION: The ClinicalTrials.gov NCT03760003 Phase 2b entry reports BLOOD only, with no rectal tissue values. The tissue that was removed is the one whose values were not corrected.

Seven months after the Phase 2b maintenance posted zeros, the Phase 2b 16 wk double blind miR-124 results posted what we infer to be inflated numbers on ClinicalTrials.gov -- the values were identical to those published in Apolit 2023. We believe the ClinicalTrials.gov unit “copies number/cell” is INCORRECT and ought to be corrected.

Sources: Apolit et al. 2023; NCT03760003 Outcome 16 (Cataldi, 14 November 2025); NCT04023396 Outcome 10 (Desroys du Roure, 27 April 2025); Scorpion Capital analysis, modeling, estimates, and literature/publication review

Phase 2b induction draft history on ClinicalTrials.gov shows the registry's quality control review questioned the blood miR-124 outcome: "The measure does not appear to include sufficient information to understand how outcomes are measured and reported." ABVX later replaced all eight blood values and deleted the rectal endpoint in the same submission -- five results submissions were returned to draft before the final record posted.

NCT03760003 (ABX464-103), results submission history. Six submissions between 17 May 2024 and 14 November 2025, five were returned to draft. The quoted comments are from ClinicalTrials.gov quality-control review by the National Library of Medicine.

RECTAL BIOPSY

Submitted	What Abivax filed	Registry response
17 May 2024	Filed as "miR-124 Expression in Rectal Tissue", unit "Fold change from baseline". Week 8: 1.78, 24.48, 65.85, 218.2. Week 16: 3.35, 39.29, 94.05, 18.19. n = 64, 63, 61, 64.	Reset. Rectal not flagged
31 Jul 2024	Same title, same unit, same eight values. n changed to 33, 32, 34, 40.	Reset. Rectal not flagged
28 Nov 2024	Retitled "miRNA-124 Expression (Copy Number of RNA Strands) in Rectal Tissue at Week 8 and Week 16". Unit field still reads "Fold change from baseline". All eight values unchanged.	Reset. Rectal not flagged
27 Mar 2025	Measure removed from the record.	Reset. Cytokines and the adverse events module flagged
14 Aug 2025	Absent.	Reset. Cytokines flagged
14 Nov 2025	Absent. Posted 28 Nov 2025 with no rectal miR-124.	Cleared and posted

WHOLE BLOOD

Submitted	What Abivax filed	Registry response
17 May 2024	Filed as "miR-124 Expression in Total Blood", unit "units on a scale". Week 8: 0, 0.00008, 0.00015, 0.00023. Week 16: 0, 0.00006, 0.00013, 0.00021. n = 64, 63, 61, 64.	Reset. Blood not flagged
31 Jul 2024	Same title, same unit, same eight values. n changed to 57, 50, 56, 60.	Reset. Blood FLAGGED
28 Nov 2024	Retitled "miRNA-124 Expression (Copy Number) in Whole Blood at Week 8 and Week 16". Unit changed to "copy number". All eight values unchanged.	Reset. Blood not flagged
27 Mar 2025	Unit changed to "copies number/cell". Every value replaced. Week 8: 28.93, 4,598, 8,517, 13,753. Week 16: 23.79, 4,154, 7,723, 13,268.	Reset. Cytokines and the adverse events module flagged
14 Aug 2025	Unchanged.	Reset. Cytokines flagged
14 Nov 2025	Unchanged. Posted 28 Nov 2025.	Cleared and posted

Blood was relabeled after the comment -- its values were replaced four months later. Rectal was not questioned and its values never changed -- yet it was deleted in the same submission that replaced the blood values.

Sources: NCT03760003 record history, versions 11 to 16; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's miR-124 data is so internally contradictory and incoherent that it undermines the purported MOA: ClinicalTrials.gov shows the same blood miR-124 outcome replaced with values ~57–69 million× larger while remaining labeled as "copies/cell." Those replacement values are identical to the miR-16-normalized values published by Apolit.

This panel shows the "Compare Records" function on ClinicalTrials.gov for archived versions 13 and 14 of NCT03760003, where whole blood values filed as copy number (red, strikethrough) were replaced by the identical values Apolit publishes (green), still labeled copy number per cell -- suggesting normalized values replaced the near-zero measurements without changing the unit.

Field, as filed	Mean	Standard deviation	Added value ÷ removed value
Unit of measure	~~copy number~~ copies number/cell		
Week 8, Matching Placebo	~~0~~ 28.93	~~0~~ 146.4	undefined
Week 8, ABX464 25 mg	~~0.00008~~ 4,598	~~0.00016~~ 11,348	57,475,000
Week 8, ABX464 50 mg	~~0.00015~~ 8,517	~~0.00012~~ 6,252	56,780,000
Week 8, ABX464 100 mg	~~0.00023~~ 13,753	~~0.00022~~ 12,142	59,795,652
Week 16, Matching Placebo	~~0~~ 23.79	~~0~~ 94.69	undefined
Week 16, ABX464 25 mg	~~0.00006~~ 4,154	~~0.00007~~ 5,273	69,233,333
Week 16, ABX464 50 mg	~~0.00013~~ 7,723	~~0.00014~~ 7,477	59,407,692
Week 16, ABX464 100 mg	~~0.00021~~ 13,268	~~0.00016~~ 11,134	63,180,952

Registry QA audit, ClinicalTrials.gov/National Library of Medicine:

1. **Returned June 13, 2024, version 11. No comment on any miR-124 measure. Fifteen other items flagged.**
2. **Returned August 28, 2024, version 12. On the measure "miR-124 Expression in Total Blood": "The measure does not appear to include sufficient information to understand how outcomes are measured and reported." Record level: "Issues noted on a previous submission of this record do not appear to have been addressed."**
3. **Returned December 19, 2024, version 13. Record level: "This record has new issues that must be addressed."**
4. **Returned April 15, 2025, version 14. Record level: "Issues noted on a previous submission of this record do not appear to have been addressed."**
5. **Returned September 2, 2025, version 15. Record level: "Issues noted on a previous submission of this record do not appear to have been addressed."**
6. **Cleared November 14, 2025, version 16. Posted 28 November 2025 under the unit copies number/cell, carrying the values Apolit publishes.**

Sources: NCT03760003 record history, versions 13 and 14 -- NCT03760003 (ABX464-103), outcome measure *miRNA-124 Expression (Copy Number) in Whole Blood at Week 8 and Week 16.*; version 13 submitted 28 November 2024 and reset 19 December 2024, against version 14 submitted 27 March 2025; mean with standard deviation, n = 57, 50, 56 and 60; strikethrough on pink is the removed text and green is the added text, reproduced in the same scheme the Compare Records tab uses; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The deleted blood values closely match ABVX's absolute ddPCR data -- suggesting raw copy counts were deleted and replaced by normalized fold-change values but retained the "copies/cell" label. The removed values sit near zero like the maintenance ddPCR record; the replacements jump to 28.93–13,753 despite baseline/placebo being zero or below quantification.

The induction values removed from the ClinicalTrials.gov posting (blue), held in the audited drafts, set against those posted for the maintenance, whole blood

Dose arm	Removed[1], 8w (posted value[2])	Removed[1], 16w (posted value[2])	ClinTrials posted, 48w blood
Placebo or baseline	0 (28.93)	0 (23.79)	0.00000
ABX464 25 mg	0.00008 (4,598)	0.00006 (4,154)	NA
ABX464 50 mg	0.00015 (8,517)	0.00013 (7,723)	0.00013 (1,162*)
ABX464 100 mg	0.00023 (13,753)	0.00021 (13,268)	NA
Fold change reported	Draft, Apolit text and ClinTrials.gov	ClinTrials.gov only	*Figure only, digitized

Footnotes

[1]Filed in NCT03760003 (ABX464-103) at versions 11 (17 May 2024), 12 (31 July 2024) and 13 (28 November 2024), identical. Unit as filed was "units on a scale" at versions 11 and 12 and "copy number" at version 13. Participants analyzed (n) were 64, 63, 61, 64 at version 11 and 57, 50, 56, 60 at versions 12 and 13. Each of those versions was returned to draft by ClinicalTrials.gov quality control, so these values never reached the public record. Version 14 (27 March 2025) replaced all eight, changed the unit to "copies number/cell", and deleted the rectal measure in the same submission. The description written for these values is still attached to the posted record and reads: "0" in the placebo column means "no signal", so BLQ (Below the level of quantification).

[2]The published values. Blood week 8 appears as 28.93, 4,598, 8,517 and 13,753 in two places: ClinicalTrials.gov outcome measure 16, posted 28 November 2025 under the unit "copies number/cell", and the Apolit 2023 results text as "the mean number of copies/cell", cited to Figure 4e. Blood week 16, 23.79, 4,154, 7,723 and 13,268, appears on ClinicalTrials.gov and in no publication we could find. Blood week 48 is published only as a figure, Vermeire 2025 Figure 6B, where the median bar reads 200 off the axis and the mean of 1,162 was recovered by digitization. Neither appears as a number in the paper. The same blood week 8 data are plotted on the axis "miR-124 copies (miR16 normalized)" in Apolit Figure 4e and in the D57 panel of Figure 2 in both clinical study protocols, ABX464-104 V5.1 and ABX464-102 V7.0, which carry the byte-identical image. The protocols print n of 40, 35, 31 and 32. Apolit Figure 4e prints 59, 55, 47 and 57.

The removed induction blood values and the maintenance values posted on ClinTrials.gov agree closely. We think these are the actual ddPCR copy numbers, later inflated for reporting.

All baseline or placebo values for blood were zero. One cannot calculate a fold change from zero.

The reported values (28.93 placebo, 4,598 at 25 mg, 8,517 at 50 mg and 13,753 at 100 mg) appear twice: on ClinicalTrials.gov under the unit copies number/cell, and in the Apolit 2023 results text as "the mean number of copies/cell". We believe these are the inflated fold changes.

The maintenance posting and the 48w figure are the only direct overlap we could find, but we had to digitize the mean because no value is reported as a number, just the figure. Posted as 0.00013 against a 0.00000 baseline, the same arm at the same visit is drawn at 1,162.

Abivax state in the same filing that "0" in the placebo column means no signal, below the level of quantification. That sentence is on the posted record today, above a placebo column that reads 28.93.

Sources: NCT03760003 record history, versions 11 to 16; NCT04023396 outcome measure 10; Apolit et al. 2023; Vermeire et al. 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The rectal miR-124 endpoint was relabeled as “copy number of RNA strands” while the unit still read “fold change from baseline” -- without changing a single value, and then deleted from the final registry record. The analyzed n also roughly halved while every reported mean and standard deviation remained unchanged.

The title changed to Copy Number of RNA Strands while the unit stayed Fold change from baseline. The values did not change.

Field	Removed text, then added text
Measure title, version 12 to version 13	~~miR-124 Expression in Rectal Tissue~~ miRNA-124 Expression (Copy Number of RNA Strands) in Rectal Tissue at Week 8 and Week 16
Unit of measure, version 11 through version 13	Fold change from baseline
Participants analyzed, version 11 to version 12	~~64, 63, 61, 64~~ 33, 32, 34, 40

The eight values, identical in versions 11, 12 and 13, then gone from version 14

Timepoint	Matching Placebo	ABX464 25 mg	ABX464 50 mg	ABX464 100 mg
Week 8	~~1.78 ± 2.2~~	~~24.48 ± 24.85~~	~~65.85 ± 203.4~~	~~218.2 ± 1003~~
Week 16	~~3.35 ± 4.23~~	~~39.29 ± 85.93~~	~~94.05 ± 149.1~~	~~18.19 ± 23.67~~

Struck on red because version 14, submitted 27 March 2025, removed the measure in full. The same submission replaced every blood value.

Tables are from NCT03760003 (ABX464-103) -- the rectal miR-124 outcome measure across its three filings, and its removal. Mean with standard deviation. Strikethrough on red is removed text and green is added text, as rendered by the Compare Records tab.

Notes: The rectal numbers were filed three times and never altered. 1.78, 24.48, 65.85, 218.2 at week 8 and 3.35, 39.29, 94.05, 18.19 at week 16 appear identically in the submissions of 17 May 2024, 31 July 2024 and 28 November 2024. The number stayed the same while the label changed. Version 13 renamed the measure to "miRNA-124 Expression (Copy Number of RNA Strands) in Rectal Tissue at Week 8 and Week 16" while leaving the unit field reading "Fold change from baseline". The title says copy number of RNA strands. The unit says fold change. Both were on the record at the same time, describing the same eight numbers. The participant count moved too. Version 11 gave 64, 63, 61 and 64. Version 12 gave 33, 32, 34 and 40 for the same eight values. Roughly half the denominator, with no change to any mean or standard deviation. Version 14 deleted the measure. Rectal miR-124 does not appear in the record that posted on 28 November 2025.

Sources: NCT03760003 record history; versions 12 and 13; versions 13 and 14; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's rectal-biopsy miR-124 values cannot be reconciled across sources -- registry drafts, Apolit and absolute maintenance ddPCR report incompatible numbers and units. At 50 mg, the same clinical program reports 65.85-fold in the deleted registry draft, 8,347 "copies/cell" in Apolit and 0.00255 copies/cell by maintenance ddPCR.

The induction values were filed as fold change from baseline, remained identical through three drafts, then were deleted before the record was posted. At 50 mg, the deleted 65.85-fold value is ~25,800× the maintenance ddPCR value, while Apolit's 8,347 "copies/cell" is ~3.3 million× higher. These cannot all represent the same underlying miR-124 measurement.

The induction values removed from the ClinicalTrials.gov posting, visible in the audited drafts, compared to those posted for the Maintenance, rectal and sigmoidal miR-124

Dose arm	Removed[1], 8w (published value[2])	Removed[1], 16w (no published value)	ClinTrials posted, 48w rectal	ClinTrials posted, 48w sigmoidal[3]
Placebo or baseline	1.78 (746)	3.35	0.00065	0.00035
ABX464 25 mg	24.48 (8,345)	39.29	NA	NA
ABX464 50 mg	65.85 (8,347)	94.05	0.00255	0.00225
ABX464 100 mg	218.2 (9,171)	18.19	NA	NA
Fold change reported	Draft and Apolit text and figure	NR	Figures only	NR

Footnotes

[1]Filed in NCT03760003 (ABX464-103) at versions 11 (17 May 2024), 12 (31 July 2024) and 13 (28 November 2024), identical in all three. Unit as filed was "Fold change from baseline," and it was never altered. Participants analyzed (n) were 64, 63, 61, 64 at version 11 and 33, 32, 34, 40 at versions 12 and 13, with no change to any mean or standard deviation. Version 13 retitled the measure "miRNA-124 Expression (Copy Number of RNA Strands) in Rectal Tissue at Week 8 and Week 16" while the unit field continued to read fold change. Each of those versions was returned to draft by ClinicalTrials.gov quality control, so these values never reached the public record. Version 14 (27 March 2025) deleted the measure in full, in the submission that replaced every blood value. The registry reviewer raised the rectal measure in none of the five returns.

[2]The published values. Rectal week 8 appears as 746, 8,345, 8,347 and 9,171 in the Apolit 2023 results text, cited to Figure 4b, under the unit copies per cell. The axis on Figure 4 panels a and b reads "miR-124 copies (miR16 normalized)". The rectal fold-increase panel, Figure 4c, carries p values and no number, and no bar is drawn in it. Rectal week 48 is published only as a figure, Vermeire 2025 Figure 6A, where the median of 4.89 and the mean of 27.6 were recovered by digitization and appear nowhere that we could find. Figures comprising the rectal data are given with no corresponding values in Apolit Figure 4c, Vermeire 2025 Figure 6A, the Santo UEGW 2023 poster, and the Abivax corporate presentations of 19 March 2025 (slide 12) and May to December 2025 (slide 11). The clinical study protocols plot a third quantity. ABX464-104 V5.1 Figure 1 and ABX464-102 V7.0 Figure 1 are the byte-identical image, a single D57 panel on the axis "Total copies miR124.1 (DNA normalized)" running 0.01 to 100, n = 42, 44, 37 and 43, three orders of magnitude below the copies per cell the paper reports for the same tissue at the same visit.

[3]Sigmoidal biopsy appears in no version of NCT03760003, in the results sections or in the prespecified outcomes, across all 17 archived versions. Nothing was removed. It is filed only in NCT04023396 and reported as fold change at week 8 in the Phase 3 ABTECT posters.

The rectal metric was filed under the unit fold change from baseline, uncorrected across versions and then deleted. The title changed on version 13 - it became Copy Number of RNA Strands. Thus, Version 13 held both units on the record simultaneously to describe the same dataset. The units cannot be both ddPCR and fold-change.

The maintenance baseline was 0.00065, not zero, so a fold change can be computed without substituting (3.9 rectal, 6.4 sigmoidal). Apolit published that as 8,347 (units conflated).

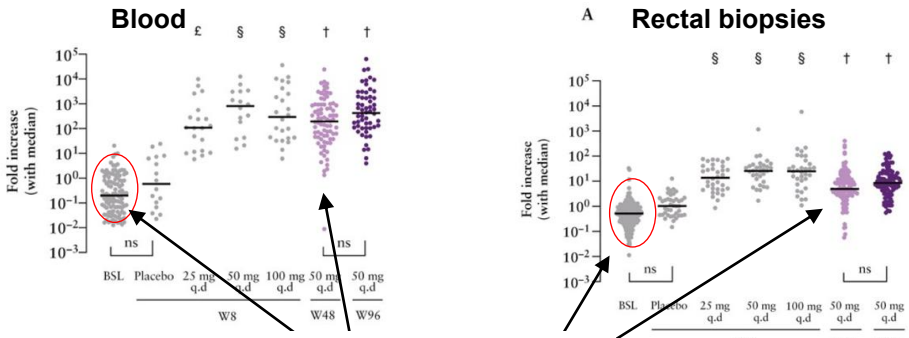
Apolit publishes the rectal 8w as 746, 8,345, 8,347 and 9,171 copies per cell (units conflated). The deleted registry draft carries numbers labeled 'fold change', 1.78, 24.48, 65.85 and 218.2 that do not agree with Apolit's numbers.. Neither set agrees with the 48w biopsy numbers of 0.00065 vs. 0.00225 (3.9-fold).

Sources: NCT03760003 record history, versions 11 to 16; NCT04023396 outcome measure 10; Apolit et al. 2023; Vermeire et al. 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's canonical miR-124 figure lacks basic statistical credibility – it compresses 3–4 orders of magnitude onto a log axis, obscuring extreme skew, near-zero observations and missing data. This figure appears across posters, manuscripts and investor presentations; medians are drawn on the graph while higher arithmetic means are emphasized elsewhere.

The graph shows the combined miR-124 metrics (fold increase) from the same ClinTrials postings. The data are on a log scale, unusual for response curves, and the spread is 3-4 orders of magnitude. The baseline and 48w point are also given on Clintrials, but not in the text. We digitize those next..

Phase 2b miR-124 figures published in presentations, manuscripts, study protocols[1]



We have these numbers by ddPCR from the 2b OLE – they are ~zero but here they are quite large

RED FLAGS On a log scale the 48 and 96w points look similar, but they drop as a set vs week 8, a pattern in both blood and rectal biopsy, suggesting a batch effect. Analysis of clinical samples for a secondary clinical endpoint should be conducted under GLP/GCP. Batch effects indicate a poorly validated assay procedure.

RED FLAGS

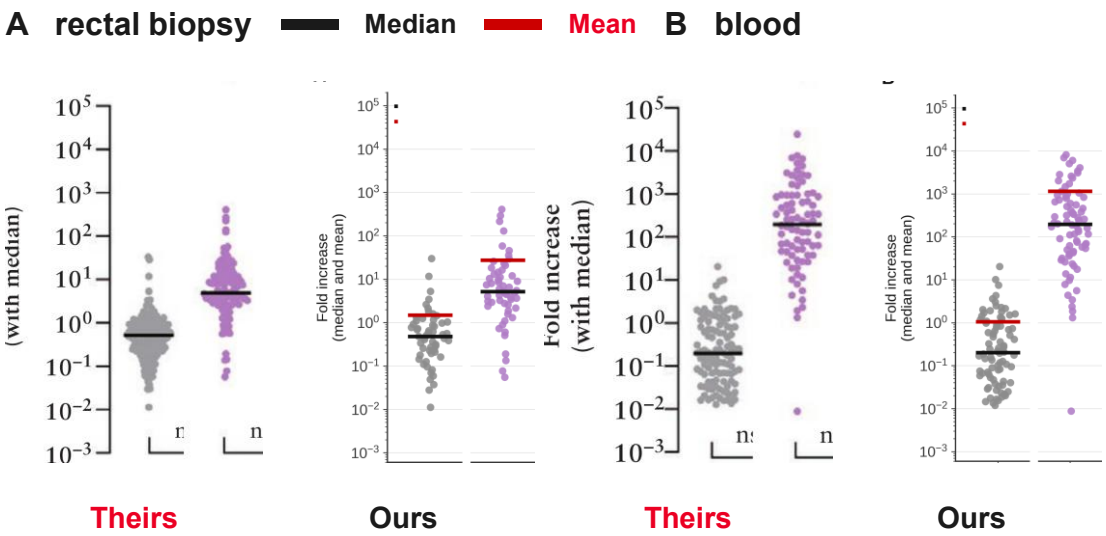
1. **Fold-change is plotted on a log scale, compressing 3–4 orders of magnitude of dispersion and visually minimizing near-zero observations.**
2. **The variance is huge, 3-orders of magnitude, and a large fraction of points are close to zero, an issue obscured by the log scale which has no zero.**
3. **The bisecting line is the median, but mean is reported in the text. No 'n' is provided. The plots in Apolit show roughly 2/3rds of the points are missing from the fold-change panel.**
4. **The baseline and Placebo numbers should be roughly equivalent, but they differ by 10-fold, obscured by the log scale.**
5. **The graph says fold-change, but the text also describes these numbers as copy number per cell and a conflates the terms across the paper, in Apolit 2017**
6. **The 16-week point is missiong and reported no where that we could find.**

[1]This figure appears in four places: the Santo et al. UEGW 2023 poster (the original), Vermeire et al. 2025 Figure 6, the Abivax corporate presentation of 19 March 2025 (slide 12), and a corporate presentation verion(s) that appear(s) to have been used subsequently in 2025 (slide 11). Clinical study protocol ABX464-104 carries no fold-change figure we could find.

Source: https://clinicaltrials.gov/study/NCT03760003; https://clinicaltrials.gov/study/NCT04023396; https://doi.org/10.1016/j.cell.2007.04.040; https://doi.org/10.1093/nar/gkw116; https://doi.org/10.1186/gb-2009-10-6-r64; https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf ; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's normalization turns essentially zero miR-124 into a massive clinical "signal" -- 0.00013 copies/cell becomes 1,162-fold, an ~8.9 million× inflation

The resulting Phase 2b fold-change values are repeated across investor decks, manuscripts and other materials. In blood, the absolute ddPCR baseline is 0.00000 copies/cell, so the fold-change denominator is undefined; in biopsy, tiny absolute counts are magnified thousands-fold. The "signal" is therefore driven by normalization of values at or near the detection floor, not by meaningful levels of miR-124.



We digitized the plots as shown below and compared baseline and week 48 timepoints fold-change with the ddPCR absolute copy number per cell posted on ClinicalTrials.gov (Phase 2b OLE) in the table. Mean is a red line and median, black. Method detailed below[1].

METHOD: ClinicalTrials.gov NCT04023396, the ABX464-104 maintenance study, against Vermeire et al. 2025 Figure 6 recovered from the digitized points. 50 mg once daily, week 48 (no baseline, week 48 or week 96 means are reported in the text). Digitized counts were recovered by measuring the ink in each column and dividing by the area of one isolated dot, which counts points that overlap; the method returns the drawn median to within 2%.

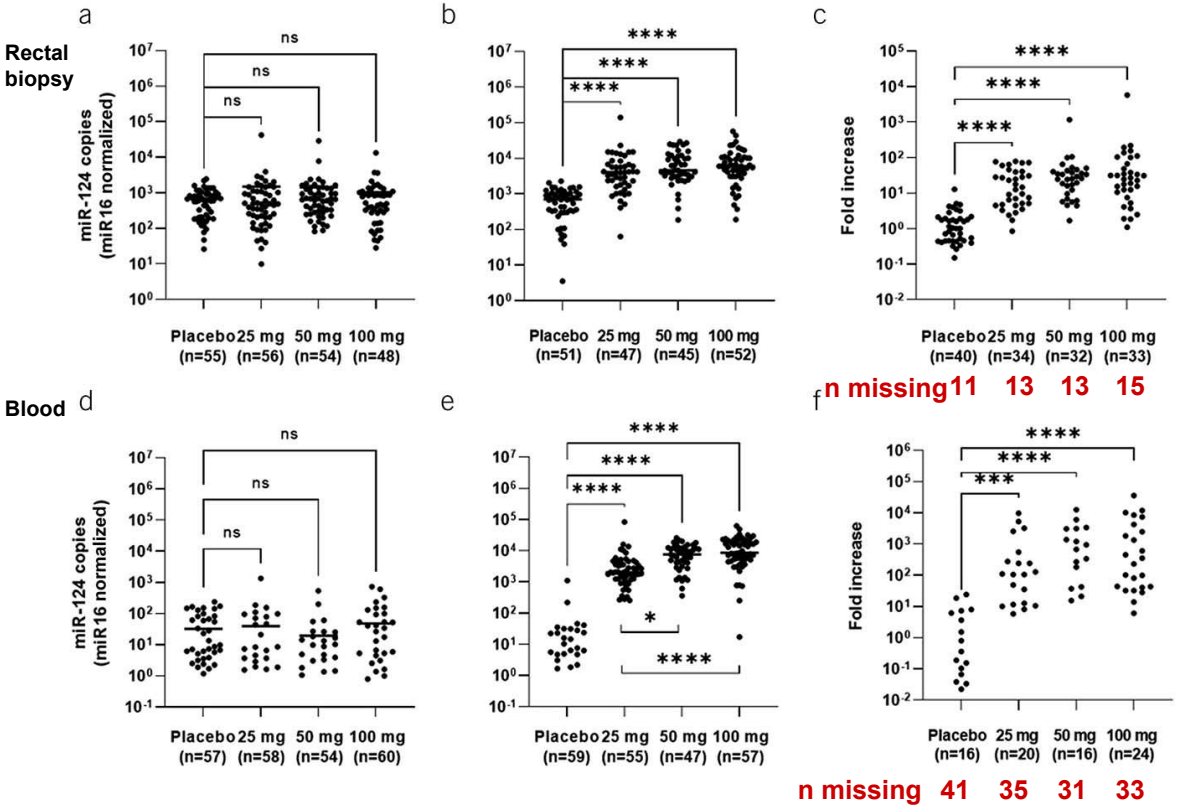
"Normalization" inflated treatment groups 3.78x more than baseline, which was already inflated 2,800x -- ridiculous signal amplification.

	ddPCR copies per cell vs fold-change, Phase 2b, 50 mg QD					
	Fold change Digitized baseline	Fold change Digitized, 48wk	ddPCR ClinicalTrials.gov baseline	ddPCR ClinicalTrials.gov 48wk	Fold Inflation, baseline	Fold Inflation, 48w
Blood	1.17 ± 2.93 (0.201)	1,162 ± 3,308 (203)	0.00000 ± 0.00000	0.00013 ± 0.00026	Unlimited, set by choice of denominator[1]	8.9 million
Rectal biopsy	1.82 ± 5.34 (0.535)	26.98 ± 71.71 (4.89)	0.00065 ± 0.00211	0.00255 ± 0.00252	2,800	10,580

[1] Blood baseline was filed as 0.00000, so the ratio has no denominator.
Sources: NCT04023396 maintenance; NCT03760003 induction; Vermeire et al. 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Key patient miR-124 values are simply omitted from Apolit's fold-change panels -- up to 65% of paired patients are absent, with no n, mean or median shown. After accounting for required baseline/week-8 pairing, 27% of rectal and 65% of blood observations are missing from the fold-change panels.

The same week-8 blood values later posted on ClinicalTrials.gov as ddPCR "copies/cell" appear in Apolit's figure, even though up to 65% of paired observations are absent from the fold-change panels.



In Apolit, Figure 4, a quarter of the rectal and two thirds of the blood patients are missing from the fold change panels, after allowing for pairing loss. The figure shows fold change with no n. The n is provided in Apolit. These are the numbers posted as ddPCR, copy number per cell on NCT03760003

Missing values and double normalizing to baseline

- **The statistical comparisons against placebo and the metrics are normalized already against placebo. Placebo cannot be normalized twice.**
- **Panels c and f carry no mean, no median and no value in the text or legend.**
- **Up to 65% of the pairs missing from d and f**

MISSING n

Panel	Placebo	25 mg	50 mg	100 mg	Missing
Rectal, panel c	11	13	13	15	52 of 191 (27.2%)
Blood, panel f	41	35	31	33	140 of 216 (64.8%)

Counted against the smaller of the baseline and week 8 panel, since a fold change needs both samples from one patient.

"MiR-124 modulation in rectal tissue (a–c) and blood (d–f) in patients with UC. The number of miR-124 copies was assessed by droplet digital PCR at baseline (a, d) and week 8 (b, e), and fold increase at week 8 compared with baseline (c, f). A total of 576 rectal biopsies from 139 patients and 1,104 blood samples from 229 patients who received ABX464 (25, 50, or 100 mg) or placebo were analyzed. Kruskal-Wallis test (P < 0.001 vs placebo; ****P < 0.0001 vs placebo)."***

Sources: Apolit et al. 2023 -- Figure 4e, blood week 8, text: 28.93, 4,598, 8,517, 13,753 -- ClinicalTrials.gov NCT03760003 outcome 16, blood week 8, as posted; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The same miR-124 measurement is described nine different ways across Apolit and ClinicalTrials.gov — “copies/cell,” “miR-16 normalized,” “fold change” and more. A key biomarker whose units and meaning vary this widely across the same dataset lacks basic credibility and makes it impossible to know what the reported values actually represent..

From Apolit et al. 2023, Clinical and Translational Gastroenterology 14:e00560, and NCT03760003. Axis labels are from figure image on page 6.

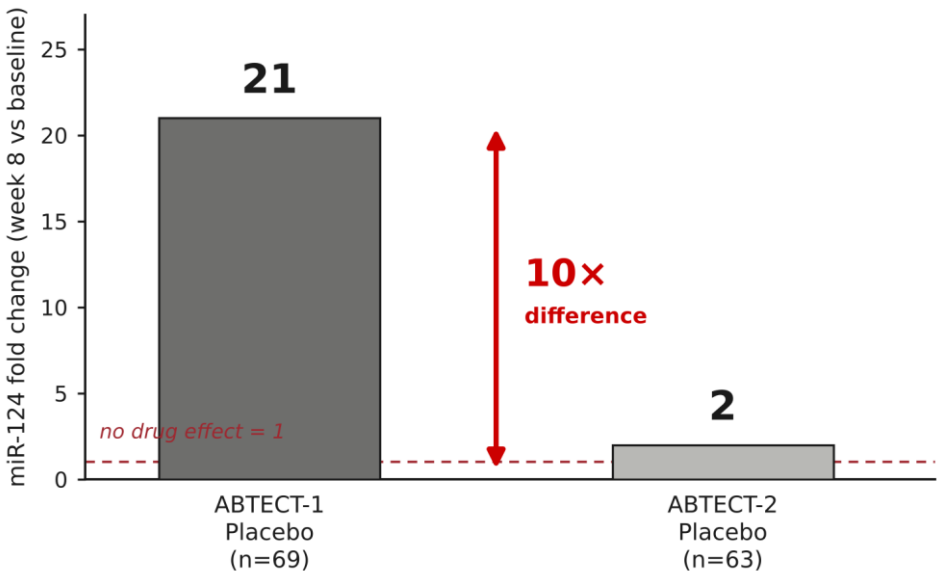
Label	Where it appears	As written
Total copy number per sample	Methods	*“The total copy number per sample was calculated by considering the total dilution factor from lysis to ddPCR, the sample-specific dilution factor for cDNA synthesis, and the cycles of preamplification.”*
Total copy number per cell	Methods	*“The total copy number per cell was calculated based on the DNA concentrations by considering the total dilution factor during lysis and extraction and the hypothesis of a 3.3-pg total weight for 1 haploid genome.”*
Normalized mir16 copy number	Methods	*“The normalized miR16 copy number was calculated using a sample-specific normalization factor that considers the relative expression of miR-16 per sample per batch.”*
Fold change	Statistics	*“The miR-124 modulation is expressed in fold change, while cellular population and cytokine secretion modulations are expressed in percentage of upregulation or downregulation.”*
The mean number of copies/cell	Results text	*“The mean number of copies/cell: placebo, 746” and twice more, for blood at baseline and at week 8*
miR-124 copies (miR16 normalized)	Figure 4 axis, panels a, b, d, e	The axis label on the four panels whose values the results text calls copies/cell
Fold increase	Figure 4 axis, panels c, f	The axis label on the two panels the results text discusses with p values and no number
The number of miR-124 copies	Figure 4 legend	*“The number of miR-124 copies was assessed by droplet digital PCR at baseline (a, d) and week 8 (b, e), and fold increase at week 8 compared with baseline (c, f).”*
copies number/cell	ClinicalTrials.gov NCT03760003	The unit field as filed, carrying the same four week 8 values the results text prints

The figure axis labels the values “miR-16 normalized,” while the text calls the same numbers “copies per cell.” The methods define both as different quantities, yet the paper never explains how one became the other..

Sources: Apolit et al. 2023; NCT03760003; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Phase 3 placebo arms disagree by 10× for miR-124 expression — they should be the same: ABTECT-1 shows 21-fold miR-124 versus 2-fold in ABTECT-2, despite the same trial design, assay and no drug. If the untreated control varies by an order of magnitude, the treatment-arm fold changes cannot credibly be attributed to ABX464.

ABTECT-1 vs ABTECT-2 PLACEBO ARMS DIFFER
10x -- Blood miR-124, baseline vs. week 8



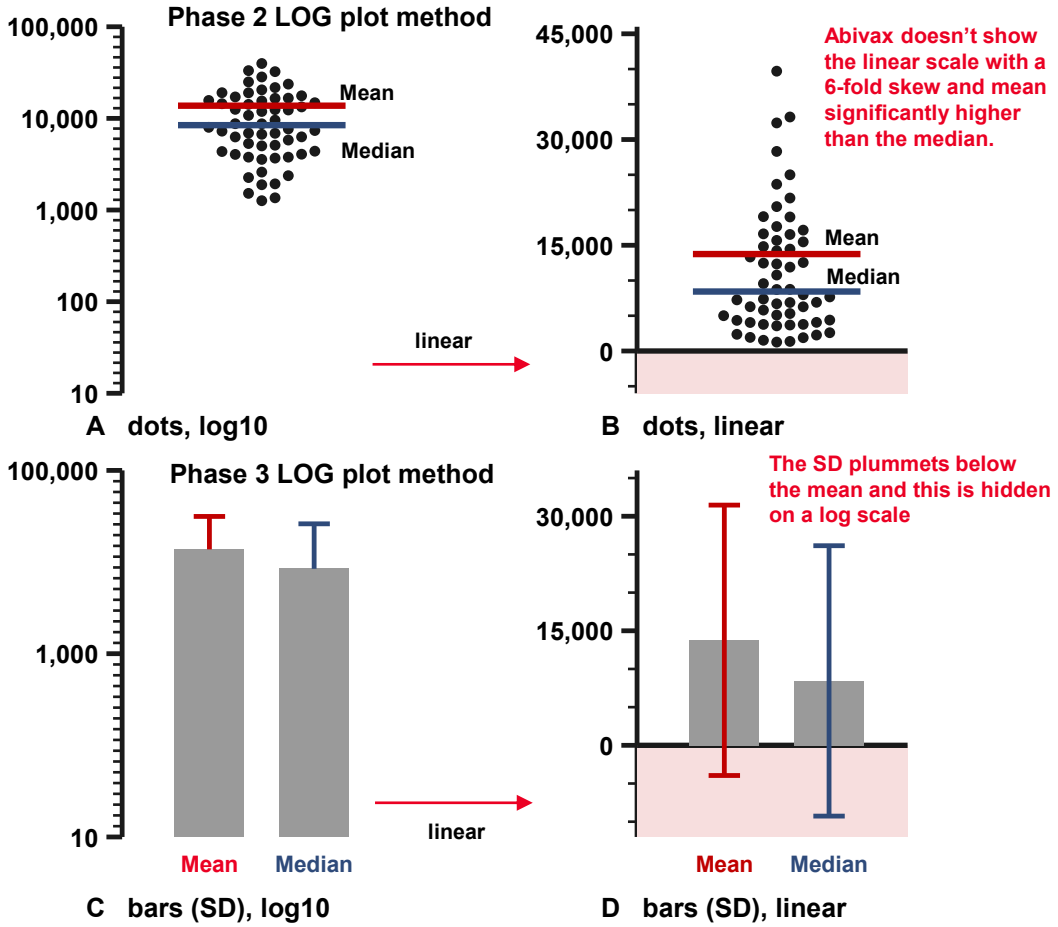
Statistical red flags -- the untreated controls expose the problem. If placebo itself moves 10×, the treatment-arm fold changes cannot credibly be attributed to ABX464

- Both placebo arms should be near 1 as it is the same trial design, same assay, and no drug.
- Instead, placebo is 21-fold in ABTECT-1 vs. 2-fold in ABTECT-2 — a 10× difference with n=69 and n=63.
- The likely problem is the denominator. Baseline blood miR-124 is at or near the detection floor, so tiny differences in baseline can create enormous fold changes.
- This makes the ratio instable. A few patients with exceptionally low baseline values can dominate the mean.
- Batch effects, assay drift or denominator instability can produce exactly this pattern.
- Additional red flag -- individual values span several-fold around each mean, and treatment and placebo distributions overlap heavily despite the reported p < 0.0001.

Sources: Siegmund et al. 2026, ECCO P0868; ABTECT-1, NCT05507203; ABTECT-2, NCT05507216; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's clinical miR-124 signal rests on statistical sleight of hand: log scales hide the skew, outliers inflate the mean, and statistical tests are used inappropriately. The miR-124 "effect" appears only when charts play games to exaggerate the apparent signal — the raw distribution lacks credibility.

miR-124 copies per cell in blood at week 8, ABX464 100 mg, phase 2b (Apolit et al. 2023, Figure 4e) – used as illustrative example



Mean	13,753
Median	8,437
Range	17 to 59,000
SD (reconstructed)	17,704
SE	2,345
CV	129%
Skew	6.0

What the log-scale presentation obscures

Extreme skew: A few large outliers pull the arithmetic mean far above the median; the log axis makes the distribution appear much more balanced.

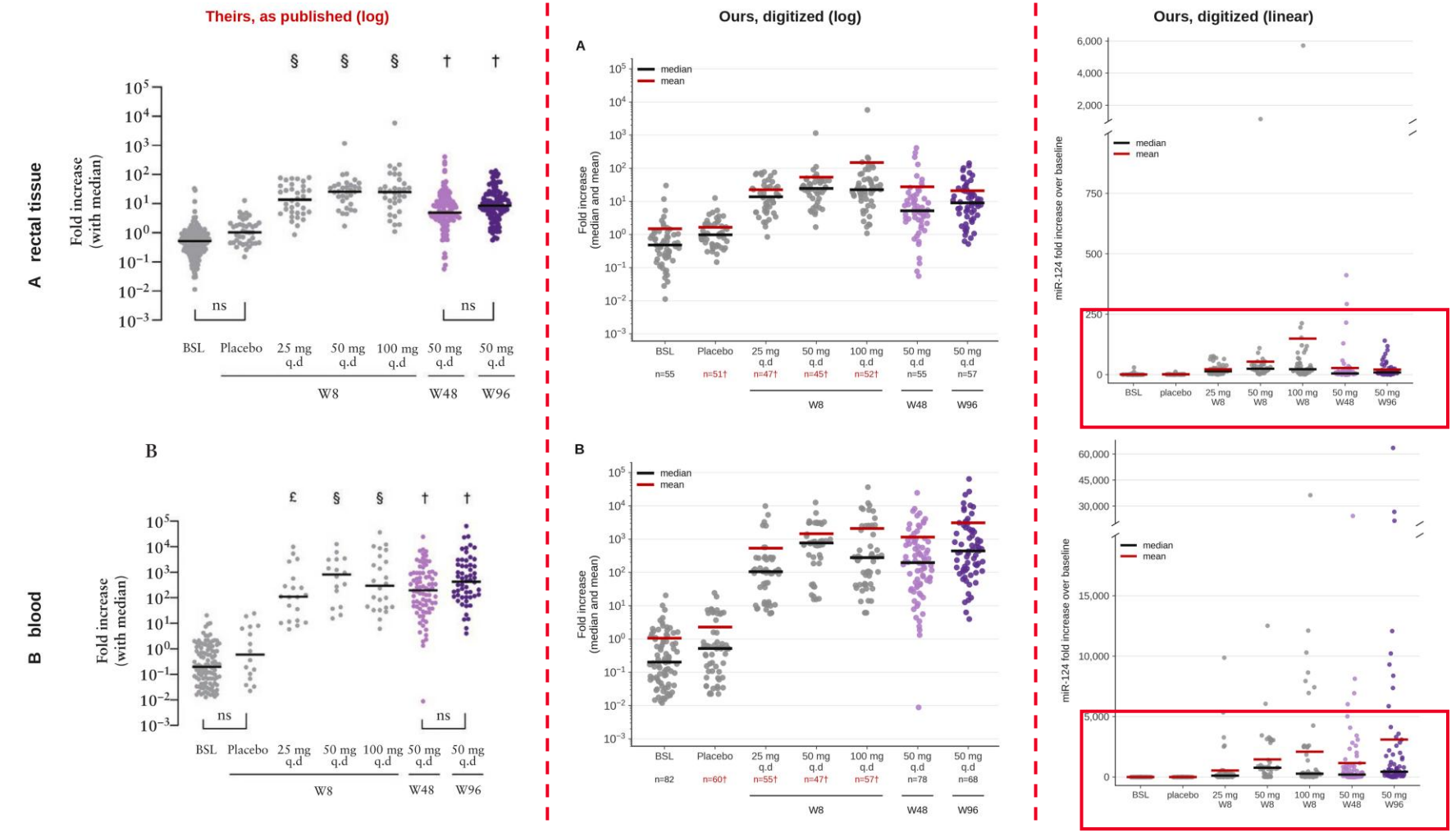
Extreme variance: SD exceeds the mean and would extend below zero on a linear mean±SD plot — something the log presentation cannot show.

Statistics don't match the headline metric: ABVX reports arithmetic means but the p-values reproduce with Dunn's rank test. Dunn's does not test the mean, so the reported effect size and significance are describing different summaries of the data.

Illustrative Phase 2b example: Mean 13,753 vs. median 8,437; SD 12,142. The raw distribution is highly skewed.

Sources: https://pmc.ncbi.nlm.nih.gov/articles/PMC10132720/; https://clinicaltrials.gov/study/NCT03760003; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our digital reconstruction of the clinical miR-124 dataset shows what the log scale hides: the miR-124 “signal” is driven by a handful of extreme outliers, while most patients cluster near zero -- on a linear scale, the signal collapses. The means (red) and medians (black) diverge sharply.



Sources: Vermeire et al. 2025; NCT03760003; Apolit et al. 2023; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's Phase 3 miR-124 "signal" appears statistically manufactured. The headline means do not produce the reported p-values -- the significance emerges only by mixing and matching incompatible statistical methods

Phase 3 miR-124 significance depends on incompatible statistical summaries: the large arithmetic means do not produce the reported p-values, but Dunn's rank test does. Eight of 12 p<0.0001 results fail to reproduce under ANOVA/Dunnett; all 12 reproduce under Dunn's. ABVX is effectively pairing the larger effect size from one framework with the stronger significance from another.

Phase 3 statistical audit: ECCO 2026 poster P0868 reported p-values vs. p-values reconstructed from the reported mean, SD and n

Panel	Dose	Mean	SD	n	p poster and corporate deck	p recomputed ANOVA, Dunnett's	p recomputed Dunn's
blood ABTECT-1	25 mg	602	1,770	71	<0.0001	0.0073	<0.0001
blood ABTECT-1	50 mg	1,035	2,351	138	<0.0001	0.0000013	<0.0001
blood ABTECT-2	25 mg	171	347	67	<0.0001	0.00017	<0.0001
blood ABTECT-2	50 mg	789	1,714	130	<0.0001	0.00000065	<0.0001
rectal ABTECT-1	25 mg	22	40.8	42	<0.0001	0.0053	<0.0001
rectal ABTECT-1	50 mg	37	75.7	62	<0.0001	0.00088	<0.0001
rectal ABTECT-2	25 mg	15	22.7	45	<0.0001	0.00040	<0.0001
rectal ABTECT-2	50 mg	58	166	61	<0.0001	0.011	<0.0001
sigmoid ABTECT-1	25 mg	32	113	80	<0.0001	0.020	<0.0001
sigmoid ABTECT-1	50 mg	33	66.2	175	<0.0001	0.0000000043	<0.0001
sigmoid ABTECT-2	25 mg	31	83.2	72	<0.0001	0.0057	<0.0001
sigmoid ABTECT-2	50 mg	42	98.1	178	<0.0001	0.00000035	<0.0001

8 of 12 fail under ANOVA/Dunnett; all 12 reproduce under Dunn's

Same Phase 3 data, different presentation: ECCO 2026 scientific poster vs. ABVX investor deck

What	ECCO poster P0868	Corporate deck, 2 Feb and 18 Mar 2026
The 18 bar values	21, 602, 1,035 and the rest	identical
The 18 sample sizes	69, 71, 138 and the rest	identical
Error bars	upper half of each drawn	all removed
p values	p<0.0001 on all six panels	removed from both blood panels, kept on the four colon panels
Axis floor	0.1	raised to 1
Axis title	none	"Mean (SD) Fold Change From Baseline"
Method stated	ANCOVA, log10 baseline covariate, Dunn's test	none stated

Notes: Dunn's values are simulated from the mean, SD and n on the poster, drawing lognormal samples and ranking them, 4,000 replicates per panel. They run from 1.9 in a million to below 1 in a thousand million means. The poster states Dunn's but the deck doesn't indicate which test.

Sources: https://www.abivax.com/wp-content/uploads/abivax-poster-P0868-Siegmund.pdf; https://www.abivax.com/wp-content/uploads/2026/04/abivax-poster-cytokines-mir-124-dulai-ddw.pdf; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our reconstruction shows that ABVX's miR-124 "signal" is smaller than its own variance and just statistical noise -- SD exceeds the mean across the clinical groups, mean minus SD falls below zero, and within-group ranges span up to 2.8 million-fold. This is incompatible with a stable, credible biological signal.

Source data: Vermeire et al. 2025 Fig. 6; Apolit et al. 2023 Fig. 4; ClinicalTrials.gov NCT03760003. Audit statistics reconstructed by Scorpion Capital from the published plots

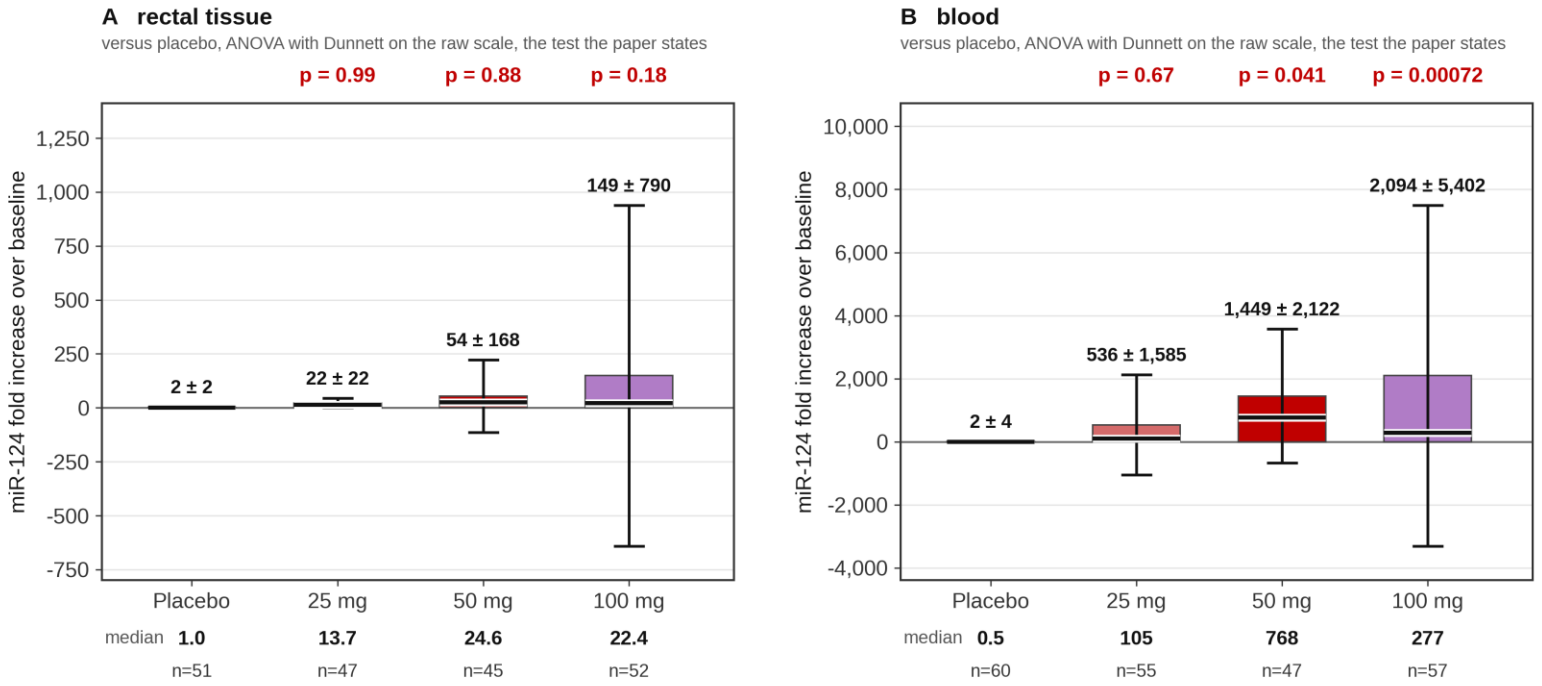
Panel	Group	Audit Median	Median	Audit Mean	SD	Range
Rectal	BSL	0.535	0.482	1.48	4.30	2,702-fold
Rectal	Placebo	1.04	0.979	1.64	1.96	86-fold
Rectal	25 mg W8	14.4	13.7	22.3	22.5	92-fold
Rectal	50 mg W8	26.5	24.6	53.5	168	689-fold
Rectal	100 mg W8	25.6	22.4	149	790	5,310-fold
Rectal	50 mg W48	4.89	5.21	27.6	73.0	7,498-fold
Rectal	50 mg W96	8.70	9.04	20.9	30.2	273-fold
Blood	BSL	0.201	0.202	1.05	2.65	1,711-fold
Blood	Placebo	0.606	0.518	2.27	4.38	1,095-fold
Blood	25 mg W8	117	105	536	1,585	1,711-fold
Blood	50 mg W8	867	768	1,449	2,122	813-fold
Blood	100 mg W8	305	277	2,094	5,402	6,016-fold
Blood	50 mg W48	203	196	1,155	3,111	2,801,571-fold
Blood	50 mg W96	459	439	3,096	8,781	16,101-fold

Methodology: Table 2. Reported and reconstructed summary statistics from Vermeire et al. (2025), Fig. 6; ClinicalTrials.gov NCT03760003, Outcome 16; and, for rectal induction data, Apolit et al. (2023), Fig. 4. Reconstructed n is the number of discrete data points recovered by digitization. Published medians were measured from the median bars in the figures. Vermeire Fig. 6 reports no mean, standard deviation or range.

Sources: https://academic.oup.com/ecco-jcc/article/19/5/jjaf074/8149142; https://clinicaltrials.gov/study/NCT03760003; https://pmc.ncbi.nlm.nih.gov/articles/PMC10132720/; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's purported Phase 2b miR-124 dose-response largely collapses if plotted on a linear scale -- the variance overwhelms the means and the entire rectal dose-response is statistically nonsignificant. The apparent "signal" is just an artifact of division at the signal floor.

Phase 2b induction miR-124, week 8 — mean ± SD on a linear scale, with published medians shown inside each bar. Scorpion Capital reconstruction from Vermeire et al. 2025, Fig. 6; Apolit et al. 2023, Fig. 4; ClinicalTrials.gov NCT03760003.



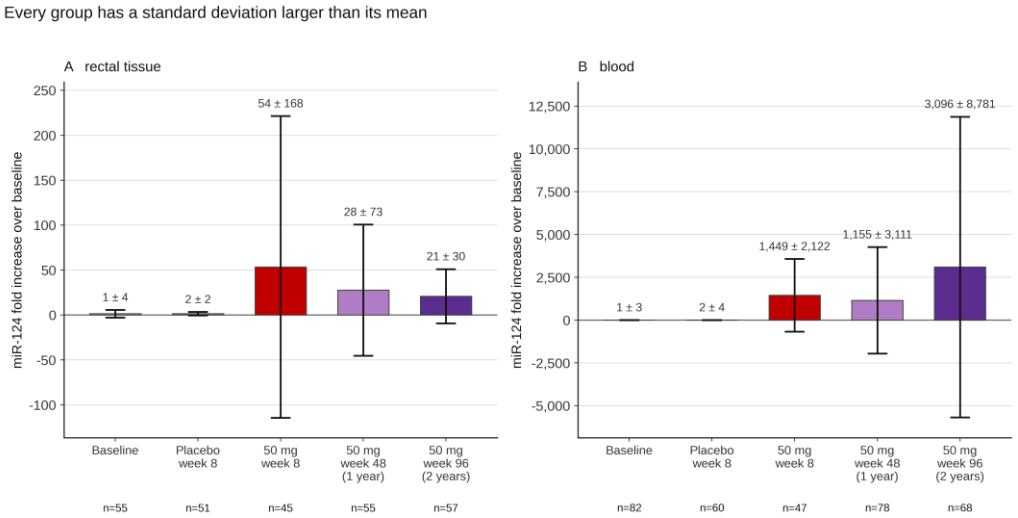
Methodology: Bars show reconstructed mean ±1 SD from values recovered from Vermeire et al. (2025), Fig. 6, using the sponsor-reported week-8 sample sizes. The black line inside each bar is the median shown in the published figure, repeated numerically below the axis. At 100 mg, the median falls below the 50 mg median in both tissues, reversing the dose ordering at the highest dose. Apolit et al. (2023) similarly reported no significant differences and no dose-dependent effect in rectal tissue. Every mean − SD interval reaches or extends below zero; negative values are impossible for a fold-change ratio.

Sources: https://academic.oup.com/ecco-jcc/article/19/5/jjaf074/8149142; https://pmc.ncbi.nlm.nih.gov/articles/PMC10132720/; https://clinicaltrials.gov/study/NCT03760003;
Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's claimed "sustained" miR-124 signal has no coherent time-response -- at the same 50 mg dose, rectal miR-124 falls after week 8 while blood ultimately rises sharply in the opposite direction. The divergent trajectories and enormous variability are incompatible with a stable, credible drug-driven biomarker.

Across week 8, week 48 and week 96, the two tissues move in different directions and every displayed SD exceeds its mean — suggesting assay instability rather than a reproducible drug-driven response..

Phase 2b longitudinal miR-124 at 50 mg — reconstructed mean ± SD in rectal tissue and blood, week 8 through week 96. Scorpion Capital reconstruction from Vermeire et al. (2025), Fig. 6; ClinicalTrials.gov NCT04023396 and NCT03760003.



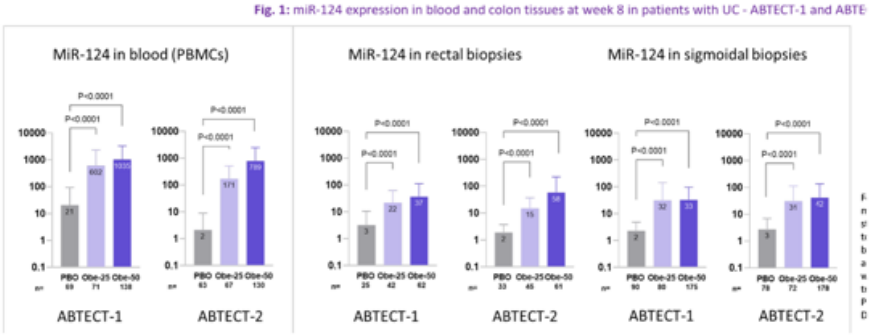
Methodology: Scorpion Capital reconstructed mean ±1 SD from Vermeire et al. (2025), Fig. 6, using the published sample sizes. Baseline, placebo and week 8 are induction data; weeks 48 and 96 are open-label maintenance at 50 mg. Week 16 blood data exist in the registry but are not shown in the figure. The black lines/labels reflect the published medians. Vermeire describes weeks 48 and 96 as sustained increases versus baseline, but the same-dose comparison from week 8 to week 48 declines in rectal tissue and does not show a coherent trajectory across tissues.

Sources: https://academic.oup.com/ecco-jcc/article/19/5/jjaf074/8149142; https://clinicaltrials.gov/study/NCT04023396; https://clinicaltrials.gov/study/NCT03760003; Scorpion Capital analysis, modeling, estimates, and literature/publication review

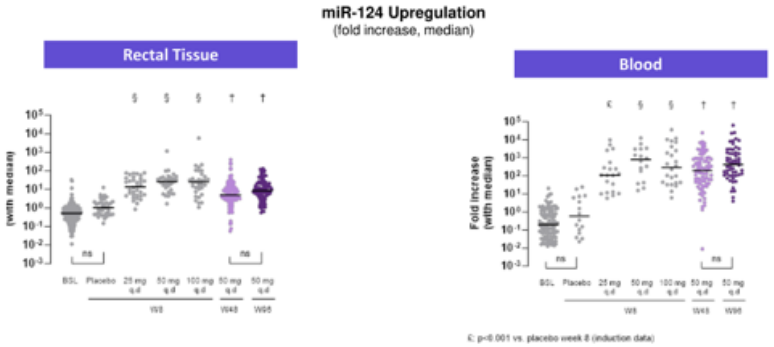
ABVX's Phase 3 miR-124 dataset contradicts itself and the Phase 2b data it claims to confirm -- the same biomarker is presented with different summaries and incompatible statistical methods, while Phase 3's own placebo arms differ 10× -- not a coherent, reproducible miR-124 signal.

Same miR-124 biomarker, different presentation: Phase 3 ABTECT vs. Phase 2b. Sources: ECCO 2026 P0868; Vermeire et al. 2025, Fig. 6; Apolit et al. 2023.

A ECCO 2026, P0868, Phase 3 ABTECT, week 8



B Abivax corporate deck 2025 (Vermeire 2025, Fig. 6)



Key inconsistencies -- ABVX presents Phase 3 as confirmation of Phase 2b, but the measurement, statistics and presentation are internally inconsistent.

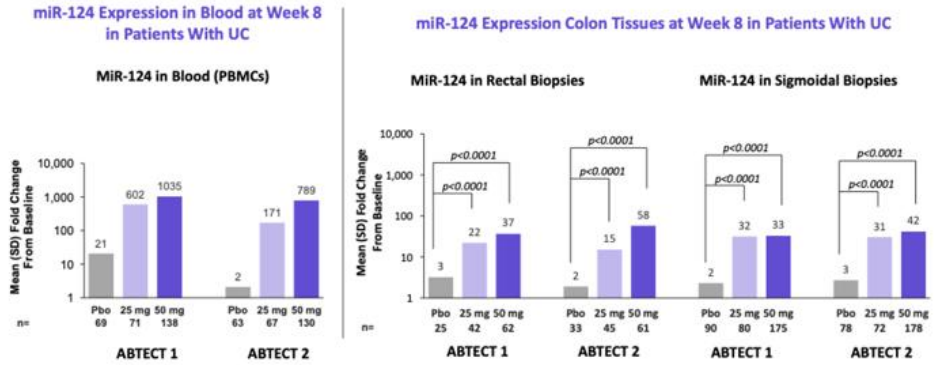
- **Placebo fails to reproduce:** Blood placebo is 21-fold in ABTECT-1 versus 2-fold in ABTECT-2.
- **Statistics are mismatched:** The Phase 3 poster presents ANCOVA-derived estimates but reports p-values from Dunn's rank test — different statistical frameworks describing different features of the data.
- **The presentation changes across phases:** Phase 3 uses bars with partial whiskers and reported means; Phase 2b shows patient-level dots and medians.
- **The sample description conflicts:** The figure says PBMCs while the methods describe whole blood.
- **Dose-response is weak:** ABTECT-1 sigmoid values are 32-fold at 25 mg and 33-fold at 50 mg, yet both are reported as p<0.0001 versus placebo

Sources: https://www.abivax.com/wp-content/uploads/abivax-poster-P0868-Siegmund.pdf; https://academic.oup.com/ecco-jcc/article/19/5/jjaf074/8149142; https://pmc.ncbi.nlm.nih.gov/articles/PMC10132720/; https://doi.org/10.1093/biomet/10.4.440; Scorpion Capital analysis, modeling, estimates, and literature/publication review

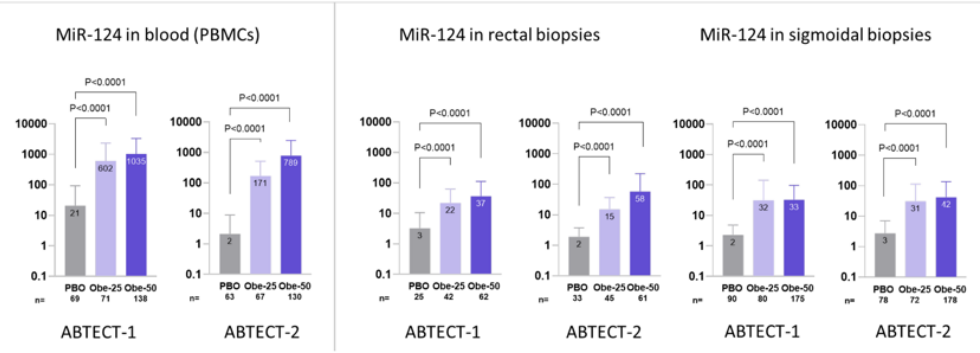
ABVX heavily sanitizes and manipulates the same Phase 3 miR-124 data for investors -- stripping out variance, methodology and blood p-values while changing the axis to make an incoherent dataset look like a credible "signal."

Same Phase 3 miR-124 data: ABVX investor deck vs. ECCO/DDW scientific posters. Sources: ABVX corporate presentation, slide 10; ECCO 2026 poster P0868 and DDW 2026 poster Tu1449

A Corporate presentation, slide 10



B ECCO 2026 poster P0868 and DDW 2026 poster Tu1449



What disappears or changes in the investor deck — the very information on variance, statistical methods and scale that makes the Phase 3 miR-124 result look unstable in the scientific posters:

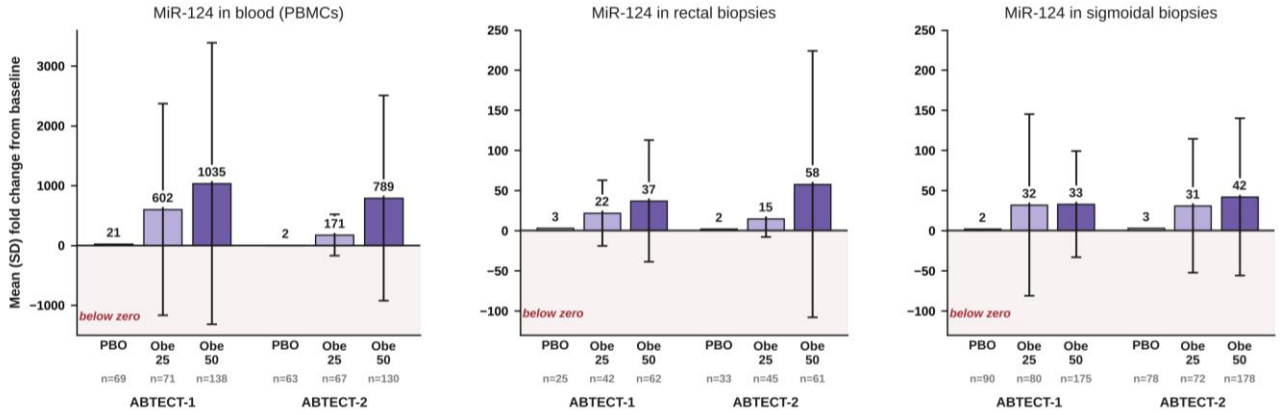
- **Error bars are removed** even though the axis labels the bars "Mean (SD)."
- **Blood p-values disappear** while the four colon p-values remain.
- **The methods footnote is removed** — including the ANCOVA model, log10 baseline covariate and Dunn's testing language.
- **The log-axis floor is raised 10×, from 0.1 to 1,** visually lifting every bar farther from baseline.
- **No linear-scale view is shown.**
- **The investor deck adds "Mean (SD) Fold Change From Baseline,"** a statistic not identified on the scientific posters.

Removed from the investor deck but disclosed in both scientific posters -- The posters state that miR-124 was quantified by ddPCR and that fold-change estimates came from an ANCOVA model using log10-transformed baseline as a covariate, while p-values were "obtained using Dunn's Test." These are different statistical frameworks: ANCOVA produces adjusted mean estimates, while Dunn's is a rank-based test and does not test those means. Our reconstruction of the reported mean, SD and n does not reproduce the stated significance under ANCOVA/Dunnett, but does under Dunn's. Thus, the displayed effect size and reported significance appear to come from different analyses.

Sources: https://www.abivax.com/wp-content/uploads/abivax-poster-P0868-Siegmund.pdf; https://www.abivax.com/wp-content/uploads/2026/04/abivax-poster-cytokines-mir-124-dulai-ddw.pdf; https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d ; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Redrawn on a linear axis, the Phase 3 miR-124 “signal” collapses -- every SD interval extends below zero, which is impossible for a fold-change biomarker and incompatible with a credible biological effect. The statistical anomalies raise serious questions of data integrity and scientific conduct.

Phase 3 ABTECT miR-124 at week 8, redrawn on a linear axis from the published posters (mean ± reconstructed SD). Sources: ECCO 2026 poster P0868 and DDW 2026 poster Tu1449; Scorpion Capital reconstruction.



What the linear redraw reveals::

- **All 12 treatment intervals extend below zero. A fold-change outcome cannot be negative, so the published summary statistics describe an incoherent distribution.**
- **SD exceeds the mean in every treatment group. For example, blood ABTECT-1 at 50 mg is 1,035 ± 2,351.**
- **The blood placebo arms differ 10× — 21 in ABTECT-1 versus 2 in ABTECT-2 — showing instability in the assay or denominator rather than a reproducible drug effect.**
- **The apparent colon signal largely disappears next to blood once the same data are shown on a linear scale.**

What the published log-axis presentation hides:

- **The log scale compresses extreme dispersion and makes unstable bars look orderly.**
- **The posters draw only the upper half of each error bar, obscuring that the implied lower half falls below zero.**
- **The investor deck removes error bars entirely and never shows a linear-scale version.**
- **Together, these presentation choices make a noisy, incoherent dataset look like a clean biomarker signal.**

Methodology: Bar heights, sample sizes and dose labels were taken directly from the published ECCO 2026 and DDW 2026 poster figures. Standard deviations were reconstructed from the upper whiskers shown on the posters; because the posters draw only the upper half of each error bar, the lower half is mirrored here for clarity. No measurable placebo whisker was recoverable from the published figure, so no placebo SD is shown.

Sources: ECCO 2026 poster P0868 (Siegmund); DDW 2026 poster Tu1449 (Dulai); Abivax corporate presentation, 2 February and 18 March 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's miR-124 assays and reporting omit basic safeguards designed to prevent exactly these red flags -- including key elements of the widely used MIQE and dMIQE reporting standards for quantitative and digital PCR, which function as quality-control checklists for peer-reviewed publication.

These omissions are a major red flag because ABVX's entire miR-124 claim depends on resolving signals at or near the detection floor and then normalizing them by additional small or unstable quantities — precisely where assay validation, detection limits and transparent normalization are most critical.

MIQE 2.0: Revision of the Minimum Information for Publication of Quantitative Real-Time PCR Experiments Guidelines FREE

The Digital MIQE Guidelines Update: Minimum Information for Publication of Quantitative Digital PCR Experiments for 2020

- **Reference / normalization stability:** ABVX normalizes to miR-16 but does not demonstrate that the reference signal is stable across the relevant disease, tissue and treatment conditions; published literature reports miR-16 modulation in inflammatory disease**.**
- **LOD / LOQ:** No clearly reported limits of detection or quantification are provided despite miR-124 measurements at or near zero. dMIQE specifically emphasizes analytical sensitivity and low-level false-positive behavior.
- **Normalization methodology:** The transformation from absolute ddPCR measurements to the reported normalized / fold-change values is not sufficiently transparent or reproducible.
- **Controls and thresholding:** dMIQE calls for disclosure of positive and negative controls, threshold-setting procedures and representative partition data — particularly important when measuring trace-level signals near the detection floor.
- **Absolute vs. normalized values:** dMIQE recommends reporting absolute concentrations even when normalized ratios are used, allowing readers to assess analytical sensitivity and denominator effects. ABVX's reporting instead emphasizes normalized / fold-change values whose relationship to the near-zero absolute measurements is unclear.
- **For the qPCR assays:** Key MIQE disclosures are also missing or insufficiently reported, including RNA-quality metrics, amplification efficiency and raw Cq information needed to assess assay performance and technical variation.

Sources: https://pubmed.ncbi.nlm.nih.gov/19246619/; https://pubmed.ncbi.nlm.nih.gov/40272429/; https://doi.org/10.1016/j.jcol.2020.05.013; https://doi.org/10.1007/s10529-010-0351-4; https://doi.org/10.1016/j.cell.2007.04.040; https://academic.oup.com/ecco-jcc/article/6/9/900/2392138; https://pubmed.ncbi.nlm.nih.gov/32746458/; https://academic.oup.com/clinchem/article/71/6/634/81191486

After auditing ABVX's full clinical miR-124 record, we find no credible evidence of meaningful, reproducible miR-124 upregulation in patients. The apparent "signal" is better explained by normalization of near-zero measurements, internally contradictory reporting and statistical artifacts.

1. **Absolute ddPCR says essentially zero.** ClinicalTrials.gov reports whole-blood baseline miR-124 at 0.00000 copies/cell and rectal values measured in thousandths of a copy per cell — incompatible with the enormous biological effect implied by the published fold changes.
2. **The reported values are internally irreconcilable.** The same clinical outcome appears under incompatible descriptions and units; blood values were replaced in the registry by numbers ~57–69 million× larger while retaining the "copies/cell" label, and those replacement values match the miR-16-normalized values published by Apolit.
3. **The apparent signal is created at the detection floor.** Tiny miR-124 measurements are normalized by another small reference signal and then divided again by a near-zero baseline. Tiny numbers divided by even tinier numbers can generate enormous fold changes without meaningful miR-124 expression.
4. **Registry history raises additional data-integrity concerns.** Values and labels change across submissions, endpoints disappear, the rectal endpoint is relabeled without changing its values, and up to 65% of paired observations are absent from key published fold-change panels.
5. **The statistical distribution is incompatible with a stable biomarker.** SD exceeds the mean across the clinical groups, within-group ranges span as much as ~2.8 million-fold, means are driven by extreme outliers, and the apparent dose-response largely collapses when shown on a linear axis.
6. **Phase 3 does not reproduce coherently.** Placebo arms differ ~10× despite no drug; rectal and blood trajectories diverge over time; and 8 of 12 reported $p<0.0001$ results fail to reproduce under ANOVA/Dunnett while all 12 reproduce under Dunn's rank test.
7. **The presentation systematically makes the signal look cleaner than the underlying data.** Log scales compress extreme dispersion; means are emphasized over much lower medians; and the investor deck removes error bars, methodology and blood p-values while raising the log-axis floor 10×.
8. **Basic assay-reporting safeguards are missing or insufficiently disclosed.** Key MIQE/dMIQE elements — including reference-signal stability, detection/quantification limits, normalization methodology, controls and thresholding — are particularly important when the purported signal sits at or near the analytical floor.

Bottom line: The clinical miR-124 evidence does not validate ABX464's purported mechanism. Across absolute measurements, registry history, normalization, statistics and Phase 3 reproducibility, the "signal" is better explained by analytical and statistical artifacts than by meaningful miR-124 upregulation — undermining the central pillar of ABX464's proposed mechanism of action.

Sources: ClinicalTrials.gov NCT03760003 and NCT04023396; Apolit et al. (2023); Vermeire et al. (2025); ECCO 2026 poster P0868; DDW 2026 poster Tu1449; MIQE/dMIQE guidelines; Scorpion Capital analysis, digitization, modeling and literature/publication review.

Chapter 15. The purported miR-124 mechanism is a molecular bait-and-switch – the real signal points to AhR activation and inactive host RNA, not selective CBC binding.

Independent Equillium data place the “miR-124” signal downstream of AhR -- an AhR antagonist reverses ABX464’s entire effect. This is at odds with ABVX’s claimed CBC binding mechanism -- AhR antagonist would not have reversed CBC action.

Using ABVX’s own RT-PCR method, GNF-351 drives ABX464’s ~7.7× signal back below control; the same assay cannot distinguish mature miR-124 from LINC00599.

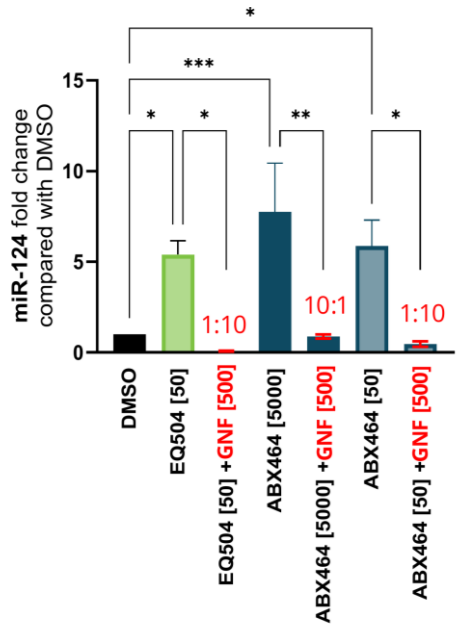


Figure reproduced from Equillium Inc., webinar 27 May 2026, slide 29. The red ratios are Equillium’s calculations.

Our digital reanalysis of the data from the figure is summarized below:

Arm	Concentration (μM)	Fold vs DMSO	Equillium’s mark
DMSO		1.0	reference
EQ504	0.05	5.1	* vs DMSO
EQ504 + GNF-351	0.05 + 0.5	under 0.5	* vs EQ504
ABX464	5	7.7	*** vs DMSO
ABX464 + GNF-351	5 + 0.5	0.85	** vs ABX464 5
ABX464	0.05	5.9	* vs DMSO
ABX464 + GNF-351	0.05 + 0.5	0.45	* vs ABX464 0.05

The assay does not distinguish LINC00599 from mature miR-124. Equillium used Abivax’s methods for the RT-PCR fold change vs DMSO.

Equillium’s RT-PCR labels the LINC00599 signal miR-124 but it is the LINC00599 host transcript. They state that they used Abivax’s methods for RT-PCR, the same methods that read the mature sequence without separating it by size. They report mature miR-124 when LINC00599, the 609 nt host transcript carrying that sequence likely comprises the signal. The assay cannot distinguish the 3 forms. In peripheral cells PTBP1 blocks Drosha cleavage, preventing formation of the 85 nt hairpin. The mature product is not made in non-neuronal cells. Thus, we conclude the assay is measuring LINC00599, downstream of AhR.

AhR appears to increase LINC00599, the 609 nt form, not miR-124 (active 20 nt form). Our audit shows it is a biologically insignificant quantity of transcript at the highest concentration measured.

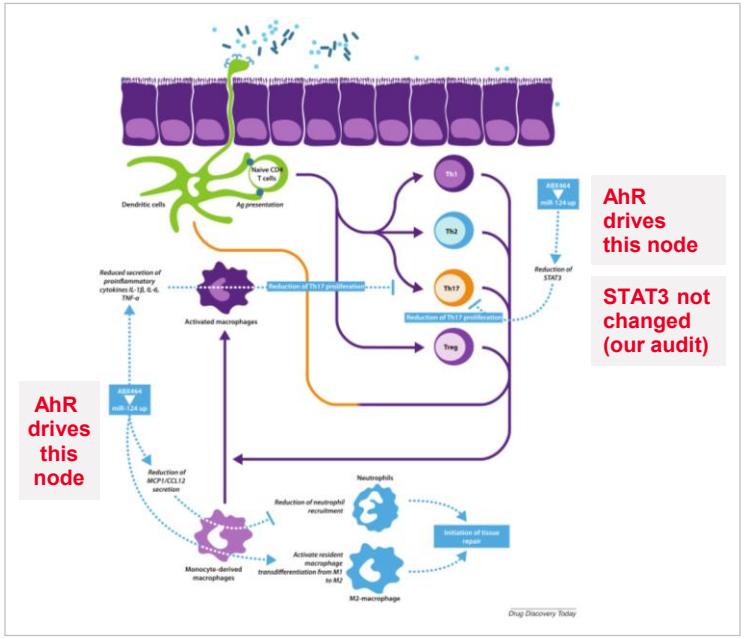
GNF-351, a competitive antagonist at the AhR, reversed miR-124 signal, decreasing the ABX464 elevation to below the DMSO control. EQ504, Equillium’s AhR agonist, produced the same reversible increase. That places the miR-124 signal downstream of AhR.

Sources: Equillium 2026, slide 29; Scorpion Capital digitization; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX co-founder Tazi's own MOA diagram is almost entirely an AhR pathway -- the lone miR-124-specific node (STAT3) is unchanged by ABX464

We audited the nodes in Tazi's 2021 diagram (below) for documented AhR activity. We confirmed that the immune effects attributed to miR-124 are actually documented AhR outputs, except STAT3, which was unchanged by ABX464 (our reanalysis of the transcriptomes). Replacing STAT3 and miR-124 nodes with AhR in Tazi's diagram below, covers the entire downstream claim set.

Tazi et al. 2021, Figure 3. "Model of the mode of action of ABX464 in the control of the intestinal immune system homeostasis."



Everything but STAT3 is downstream of AhR. Tazi says STAT3 is lowered by miR-124 (see above) but STAT3 is unchanged. Our additions to the published figure are shown in red and represent our interpretations of the datasets available.

The table shows the modulations claimed in the figure. Each effect Abivax depicts as a miR-124 output is listed with the source that establishes it as an AhR output.

Claimed by Abivax, attributed to miR-124	The AhR output
STAT3, the only one with a miR-124 recognition sequence	Not an AhR output. Unchanged by ABX464 in mouse and human transcriptomes.
IL-6, IL-1β and TNF-α	AhR (Kimura et al. 2009)
Th17 cells and IL-17A fall	AhR (Veldhoen et al. 2008; Quintana et al. 2008)
FoxP3+ regulatory T cells increase	AhR (Quintana et al. 2008)
IL-22 increases and drives tissue repair	AhR (Ishihara et al. 2022)
IL-10 increases	AhR (Zhu et al. 2018; Equillium 2026)
M1 to M2 macrophage polarization	AhR (Scorpion Capital AhR Report, Box 1)
CCL2 (MCP-1) and monocyte recruitment fall	AhR (Scorpion Capital AhR Report, Box 1)
Dendritic cell antigen presentation falls	AhR (Scorpion Capital AhR Report, Box 1)
Barrier repair and tight junction assembly	AhR (Equillium 2026)

Tazi's claim rests on STAT3 decreasing, but it is unchanged with ABX464. The deposited transcriptomes read 0.98-fold in human CD4 T cells (p 0.757) and 1.00-fold in mouse macrophages (p 0.758). Abivax continues to claim the decrease in corporate presentations. The RT-PCR assay that would measure STAT3 is run routinely by Tazi's group, and we located no document reporting those numbers.

It appears plausible to us that Abivax assigned an AhR-mediated pathway to miR-124 upregulation. miR-124 is not expressed in non-neuronal tissues. These are an AhR output, and we therefore conclude that ABX464 unequivocally stimulates AhR.

Sources: Veldhoen et al. 2008; Quintana et al. 2008; Kimura et al. 2009; Ishihara et al. 2022; Zhu et al. 2018; McGeary et al. 2019; Tazi et al. 2021; Equillium 2026; Scorpion Capital AhR Report 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's MOA story changes across Tazi-led papers: the 2019 primary data contradict the 2021 claims, without explanation – and are not reproducible

Tazi is the corresponding, senior author across the preclinical publications. The 2019 Sci. Rep. paper from his lab refutes the macrophage and Th17 claims he made in 2021 sourced to "ABIVAX, unpublished data, 2020". Apolit 2022/23 then published the data, and our audit shows that many of the p values were misreported against the displayed means – the claims therein are unsupported by the p values presented.

CLAIM	VAUTRIN 2019 *Tazi: corresponding and last author*	TAZI 2021 *"unpublished data"*	APOLIT 2022/23 *the "proof"*
Macrophages express miR-124 and ABX464 upregulates it.	miR-124 is UNDETECTABLE in monocyte-derived macrophages. ABX464 produces no upregulation. *Fig 3C, Fig S4B*	ABX464 in macrophages reduces IL-1β, IL-6, TNF-α, MCP1, CXCL1, "consistent with induction of miR-124." *p.1035-1036; ABIVAX, unpublished data, 2020*	Macrophage cytokine reduction panels presented as the proof of the MOA. The drop is so complete it can only be cell death. Abivax reported these as less significant than our audit showed. *Apolit 2023, Fig 2 / Fig 3*
ABX464 reduces Th17 / Th1 populations in PBMCs.	FACS of activated CD4+ and PBMCs from 7 donors. No change in CCR6/CXCR3 (Th17/Th1) or CD45/CCR7 subpopulations. *Fig S3*	ABX464 "significantly reduced the Th17 and Th1 populations and increased the Th2 cell population." *p.1036; ABIVAX, unpublished data, 2020*	Th17 / Th1 / Th2 / Treg panels in whole PBMCs and purified CD4+, reported p values that were insignificant by our audit. The exception was IL-17a in PBMCs. In purified CD4+ it was NS. *Apolit 2023, Fig 2c / Fig 3c*
ABX464 has direct anti-cytokine effects in immune cells.	Cytokines (IL-1β, IL-6, TNF-α, MCP1, CXCL1) not measured. No anti-inflammatory effect demonstrated in immune cells. *Whole paper; HIV-RNA splicing only*	Macrophage cytokine reductions claimed. Figure 3 schematic shows direct cytokine suppression as MOA through miR-124. *Fig 3; ABIVAX, unpublished data, 2020*	Cytokine reductions reported with quantitative values, and 16 of 23 reported p values did not reconstruct from the digitized points. 7 unsignificant comparisons were too close to change and TNFα went the wrong way. *Apolit 2023, multiplex panels*

The "unpublished data, 2020" are not only absent - they contradict the 2019 findings published by Tazi's lab under his corresponding authorship.

We infer that Apolit 2022/23 supplied the statistics for what Tazi 2021 had asserted as unpublished data. Those statistics do not reconstruct from the displayed mean points, in 16 of 17 pairs reported positive. The chronology: the published primary claims (Vautrin 2019) to the contradicted claims citing unpublished data (Tazi 2021) to Apolit, with Tazi as last author, reporting p values that do not reconstruct from the displayed data (Apolit 2022/23).

Sources: Vautrin et al. 2019; Tazi et al. 2021; Apolit et al. 2023; Scorpion Capital audit of the displayed data; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our audit of Apolit 2023 finds 16 of 23 significance marks do not reproduce from the plotted data – and 14 are reported more significant than they are

We recovered every dot in Figures 2/3 from the published PDF at 600 dpi and calibrated against the printed axis ticks. Means, standard deviations and sample sizes are from the recovered dots. p was recalculated using the two statistical tests the paper names, ANOVA with Dunnett and Kruskal-Wallis with Dunn. Change is percent change from DMSO.

Seven agree. Fourteen are reported more significant than any test the paper names supports. Two are printed less significant, and both are macrophage panels. Pink rows are printed more significant than either test supports. Sand rows are printed less significant. Grey rows agree. Cohen d is the difference between group means divided by the pooled within-group standard deviation, positive where ABX464 measured higher than DMSO. Our method was validated against mean and SD that reproduced successfully from the digitized dots.

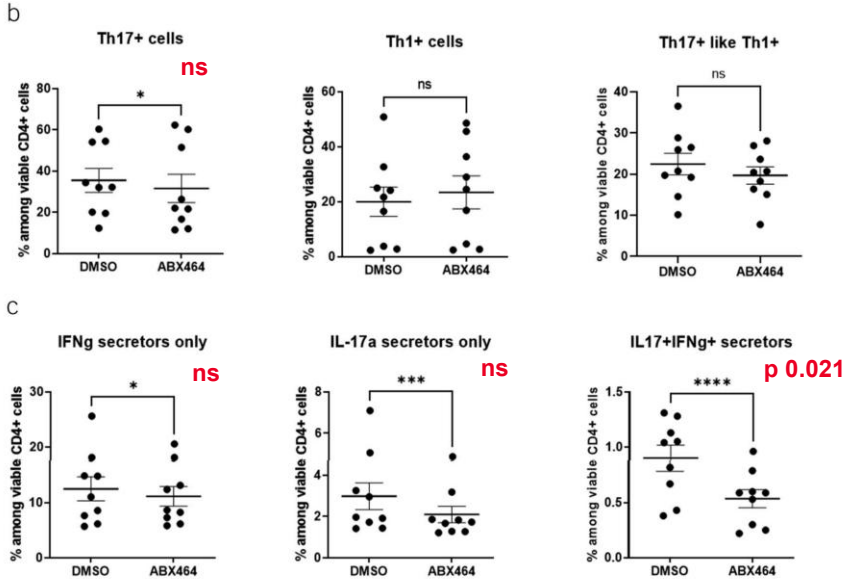
Fig	Readout	Cells	n	DMSO mean ± SD	ABX464 mean ± SD	Change (%)	p Dunnett	p Dunn	Our Audit Calculated	Printed	Cohen d
2c	IL-17a secretors	PBMC	16	3.13 ± 2.24	1.57 ± 1.56	−49.9	0.0297	0.0135	*	****	−0.81
3c	IL17+IFN-γ+ secretors	CD4+	9	0.90 ± 0.35	0.53 ± 0.25	−40.5	0.0207	0.0272	*	****	−1.21
2a	TNF-α	PBMC	16	25.28 ± 21.50	45.92 ± 44.23	+81.6	0.1036	0.2351	ns	***	+0.59
3c	IL-17a secretors	CD4+	9	2.96 ± 1.94	2.09 ± 1.20	−29.6	0.2653	0.1577	ns	***	−0.54
2a	IL-6	PBMC	16	484.89 ± 431.19	313.00 ± 255.13	−35.4	0.1801	0.2503	ns	***	−0.49
2c	IL17+IFN-γ+ secretors	PBMC	16	3.72 ± 3.06	1.37 ± 1.08	−63.1	0.0070	0.0083	**	****	−1.02
2b	Th17+ cells	PBMC	11	13.63 ± 7.31	8.14 ± 5.89	−40.3	0.0666	0.0301	*	***	−0.83
3a	IL-17a	CD4+	13	54.54 ± 50.27	31.48 ± 28.29	−42.3	0.1623	0.1997	ns	**	−0.57
2a	IL-17a	PBMC	16	87.09 ± 59.87	29.83 ± 17.24	−65.7	0.0009	0.0029	***	****	−1.30
2c	IFN-γ secretors	PBMC	16	17.58 ± 14.69	15.56 ± 16.45	−11.5	0.7165	0.1574	ns	*	−0.13
2b	Th17-like Th1+	PBMC	11	12.09 ± 9.80	10.26 ± 10.13	−15.1	0.6714	0.2643	ns	*	−0.18
3d	CCL-2	macrophage	7	14188 ± 12918	9362 ± 10209	−34.0	0.4531	0.4428	ns	*	−0.41
3b	Th17+ cells	CD4+	9	35.35 ± 17.22	31.42 ± 20.60	−11.1	0.6668	0.5365	ns	*	−0.21
3c	IFN-γ secretors	CD4+	9	12.45 ± 6.54	11.11 ± 5.32	−10.7	0.6403	0.7909	ns	*	−0.22
3b	Th17-like Th1+	CD4+	9	22.38 ± 7.93	19.59 ± 6.29	−12.4	0.4214	0.5365	ns	ns	−0.39
2b	Th1+ cells	PBMC	11	50.92 ± 11.20	53.47 ± 14.39	+5.0	0.6483	0.5994	ns	ns	+0.20
3a	IL-6	CD4+	11	44.88 ± 113.53	26.77 ± 60.64	−40.4	0.6458	0.7402	ns	ns	−0.20
3b	Th1+ cells	CD4+	9	19.92 ± 15.95	23.33 ± 17.98	+17.1	0.6760	0.6588	ns	ns	+0.20
3a	TNF-α	CD4+	12	17.72 ± 17.96	17.21 ± 11.44	−2.9	0.9345	0.7289	ns	ns	−0.03
3a	IFN-γ	CD4+	13	419.63 ± 644.36	478.61 ± 806.96	+14.1	0.8386	1.0000	ns	ns	+0.08
2a	IFN-γ	PBMC	15	1602 ± 1293	1602 ± 1272	+0.0	0.9991	0.9174	ns	ns	+0.00
3d	IL-6	macrophage	7	21848 ± 24889	1124 ± 1312	−94.9	0.0481	0.0040	**	*	−1.18
3d	TNF-α	macrophage	7	13255 ± 11068	2151 ± 1820	−83.8	0.0224	0.0072	**	*	−1.40

Sources: Apolit et al. 2023; Scorpion Capital miR-124 Report 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Apolit's purified CD4+ panels show the problem directly – Fig 3b/c FACS, four of six panels failed our audit, and one inflated value and 3 NS made significant. Sample panel is from the same paper as previous slide, where 16 of 23 p values did not pass our audit.

Th17+ cells and IL-17A secretors -- central to ABVX's proposed immune mechanism -- are marked significant in the paper but are nonsignificant in our reconstruction..

These plots are screenshots of Apolit 2023 showing cell markers by FACS in CD4 T cells. Tazi claims IL-17 cells decrease (top left) and IL-17a secretors drop but our audit showed them not significant, but marked significant on the graph.



Each panel audited against the claimed p value.

Panel and assay	Reported	Audit p	Verdict
3b Th17+ cells	*	0.667	Does not reproduce
3c IFN-γ secretors	*	0.640	Does not reproduce
3c IL-17a secretors	***	0.265	Does not reproduce
3c IL17+IFN-γ+ secretors	****	0.021	Does not reporduce
3b Th1+ cells	ns	0.676	Agrees
3b Th17+ like Th1+	ns	0.421	Agrees

Our audit indicates only one of the purified CD4 T-cell populations change. Abivax claims 4 out of 6 with p values that don't match the plotted points.

Apolit et al. 2023, Figure 3b and 3c, purified CD4+ T cells. Printed marks are the authors'. Values in red are our audit of the same plotted points.

The diagram requires Th17 (reported *, our audit NS) and IL-17a (reported ***, our audit NS) to fall in purified CD4+ cells; the plotted points show no change in either, but Apolit 2023 reported them significant. Four of the panels carry significance marks the data do not support.

Sources: Apolit et al. 2023; Tazi et al. 2021; Scorpion Capital audit of the displayed data; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The transcripts ABVX claims downstream of miR-124 carry no miR-124 recognition sequence, except STAT3 -- 19 of 20 claimed miR-124 outputs lack a conserved miR-124 target site

ABVX claims STAT3 decreases by miR-124 to modulate a central node of 'normalizing' outputs, but we found STAT3 unchanged by drug in both human and mouse transcriptomes. The deposited transcriptomes also show no coordinated repression of expressed miR-124 target-site genes — the pattern expected if mature miR-124 had meaningfully increased.

The claimed miR-124-driven outputs, 19/20 had no miR-124 recognition sequence. All are AhR outputs. The only non-AhR output claimed was STAT3, but it had a miR-124 recognition sequence and did not move in transcriptomes.

Cytokines and receptors, claimed by Abivax, AhR

IL6, IL6R, TNF, CCL2, IL10, IL22

Transcription factors, claimed by Abivax, AhR

RORC, RORA, FOXP3

Macrophage polarization markers, claimed by Abivax, AhR

NOS2, ARG1, MRC1, CD163

Signaling and silencing machinery, claimed by Abivax, AhR

ARNT, RELB, JAK1, JAK2, SOCS3, RESTI

Each gene was checked against the expressed conserved target list. None of the targets listed above contained the recognition sequence for miR-124.[1]

microRNA binds to an 8 nt recognition sequence of the transcript's UTR. Transcriptomes can be scanned for that sequence and the gene identifier for each gene. The transcripts Abivax credits to miR-124 carry no recognition sequence.

miR-124 recognition-site-positive transcripts were unchanged by ABX464 in both transcriptomes. Increased miR-124 should decrease them.

Gene	Human CD4 T cells GSE116073 fold (p)	Mouse macrophages (BMDM), no LPS GSE97062 fold (p)	Mouse BMDM, LPS GSE97062 fold (p)
STAT3	0.98 (0.757)	1.00 (0.758)	1.13 (0.150)
AHR	1.11 (0.385)	1.05 (0.449)	0.83 (0.063)
RELA	0.96 (0.422)	1.00 (0.924)	1.05 (0.285)
PTBP1	0.97 (0.541)	0.90 (0.021)	0.98 (0.188)

Four transcripts (table, above) that carry the recognition sequence were unchanged by ABX464 treatment in both transcriptomes.[2]

STAT3 carries the miR-124 recognition sequence, but its expression was unchanged by ABX464 across the transcriptomes we surveyed.

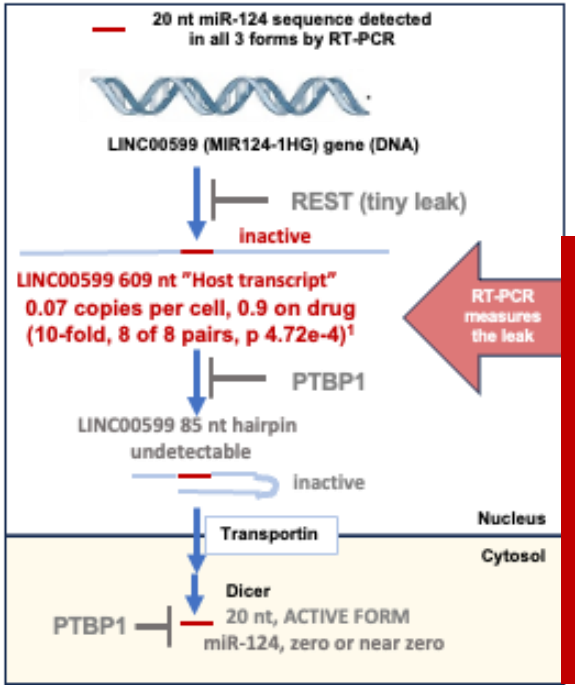
AHR carries the miR-124 recognition site. ABX464 moved it up in both unstimulated sets. Had miR-124 increased, AHR should have decreased.

PTBP1 moved 10 percent down in unstimulated mouse macrophages (p = 0.021), too small a change to carry the silencing Abivax describes.

1. Target calls are TargetScan 8.0 conserved sites for miR-124-3p.1. Of 1,820 conserved targets, 1,364 reach 1 CPM in all eight libraries of GSE116073 and those were tested for the recognition sequence. Counts were converted to counts per million on each library, a pseudocount of 0.05 CPM added, and a log2 ratio taken for each of the eight ABX464 pairs (four donors, two infection states). The change is 2 raised to the mean of those eight ratios. The p value is a two-sided paired t test on the ratio pairs (treated vs vehicle).
2. Across the full expressed set, 884 of 1,364 targets increased and 480 decreased, mean change 1.046. A microRNA acting on these transcripts would move the genes down as a set.

Sources: Zhao et al. 2016; Chebli et al. 2017; Wei et al. 2013; McGeary et al. 2019; Vautrin et al. 2019; Tazi et al. 2021; GSE116073; GSE97062; Scorpion Capital original analysis of the deposited counts; Scorpion Capital audit of the displayed data; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's RT-PCR cannot distinguish miR-124 from its host transcript LINC00599 – and miR-124 expression is held near zero at multiple checkpoints. The assay reads a sequence shared by the RNA forms; our reanalysis indicates that the detectable drug-induced species is LINC00599, at less than one transcript per cell – biologically negligible.



miR-124 processing is blocked at multiple checkpoints in non-neuronal cells. Each checkpoint is a separate mechanism keeping miR-124 expression near zero. Our audit shows Abivax measures the 609 nt host transcript and conflates that with active miR-124.

Silencing mechanisms are redundant in peripheral cells because miR-124 is a microRNA that provides neuronal attributes by silencing the non-neuronal signals.

Transcription	**REST and its binding partners close chromatin and stall RNA polymerase II. All but a tiny fraction of LINC00599 609 nt transcription is blocked at DNA, less than a copy per cell leaks through REST. At or below noise, the leak appears to increase with AhR (via ABX464) in some preparations. At these levels the product would be biologically inert even if it were processed to the cytoplasmic mature form.**
Hairpin formation	**Processing to the 85 nt stem-loop is blocked, and it draws on a precursor pool of under one copy per cell. The 609 nt form is therefore the species the assay reads.**
Maturation	**Mature miR-124 is not formed. PTBP1 blocks activity if any escapes the earlier blocks. The cell goes to extraordinary lengths to keep miR-124 silent outside neurons.**

Our reanalysis of the 32 deposited gene-count files, GSE116073, ABX464 to DMSO in HIV infected and uninfected donors, library totals 20.3 to 67.3 million. LINC00599 returned 3 to 35 reads per library (vehicle) and 66 to 835 (ABX464), or 0.372 and 4.617 CPM. Counts were converted against each library total, a pseudocount of 0.05 CPM was added, and a log2 ratio was taken for each of the eight ABX464 matched pairs. Change is 2 raised to the mean of the eight log2 ratios. P values were from two-sided paired t tests. Copies per cell were normalized against 200,000 mRNA molecules per activated CD4+ T cell (Wolf 2020). giving 0.074 copies per cell in vehicle and 0.923 with ABX464, a highly significant 10-fold change that is meaningless at less than 1 copy per cell. The libraries were poly(A) selected, so only the spliced 609 nt host transcript presents the sequence. These levels represent small quantities of leaked LINC00599.

Sources: Conaco et al. 2006; Visvanathan et al. 2007; Makeyev et al. 2007; Xue et al. 2013; Shan et al. 2016; Yeom et al. 2018; Fu et al. 2019; Equillium 2026; Wolf et al. 2020; Scorpion Capital miR-124 Report 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's own human RNA-seq shows that the entire drug-induced "miR-124" signal is the host transcript LINC00599 -- not mature miR-124. Our audit found LINC00599 elevated in 8 of 8 donor pairs, unreported, with a 10-fold increase ($p < 0.00047$) but <1 copy per cell – a biologically negligible level.

LINC00599 was the only relevant miR-124–locus RNA captured by the preparation: mature 20-nt miR-124 and its 85-nt precursor were excluded by the poly(A)-selected mRNA workflow.

We mined transcriptome-annotated miR-124 loci, human CD4 T cells

Locus	Class	DMSO (CPM)	ABX464 (CPM)	Change
MIR124-2	miRNA	0	0	not testable
MIR124-3	miRNA	0	0	not testable
MIR124-2HG	lncRNA	0.000	0.000	not testable
MIR124-1	miRNA	absent	absent	not in matrix
MIR124-1HG (LINC00599)	lncRNA	0.372	4.617	10-fold

MIR124-2 and MIR124-3 had zero reads in each of the 32 libraries, as expected. MIR124-2HG returned one read in total, 0.000 CPM.[1] MIR124-1 was not present under its current Ensembl identifier[2]. In contrast, LINC00599 increased in 8 of 8 donor pairs, p 4.72e-4, FDR 0.0625, rank 188 of 24,957 expressed genes[3]. The drug arm ran 66 to 835 reads, we estimate <1 copy per cell[4].

Our analysis, LINC00599 ratio vs DMSO

Arm	CPM	Fold	p	Pairs up
DMSO	0.372	–	–	–
ABX464	4.617	10.00	4.7e-4	8 of 8
Darunavir	0.391	1.00	0.98	4 of 8

The 10-fold increase with ABX464 was highly significant and biologically meaningless. Abivax did not report these results, we mined them from the deposited transcriptome.

The CD4 libraries were processed using the Illumina TruSeq stranded mRNA kit, which captures only polyadenylated RNA. Neither the mature 20 nt miR-124 nor the 85 nt hairpin carry a poly(A) tail and both are therefore excluded from the library. Only the polyadenylated host transcript LINC00599 remains, therefore it comprised the entire signal in this library. We believe Abivax measures the host transcript and conflates that with active miR-124. These findings are not reported or discussed, as far as we could discern.

[1] MIR124-2 and MIR124-3 returned zero reads in each of the 32 libraries, which is the expected result for a poly(A) selected library. A mature miR-124 carries no poly(A) tail and does not enter such a library, therefore these rows establish what the assay can measure. MIR124-2HG, which is polyadenylated and therefore captured, returned one read.

[2] Loci were matched by Ensembl identifier: MIR124-1 ENSG00000284321, MIR124-2 ENSG00000207816, MIR124-3 ENSG00000207598, MIR124-1HG ENSG00000253230, MIR124-2HG ENSG00000254377. The deposited matrix carries 60,448 identifiers with no gene symbols. MIR124-1 holds a re-minted identifier, therefore its absence is consistent with the annotation release used in 2018 rather than with a removal, and it may be present under a retired identifier.

[3] Counts are the 32 deposited gene-count files of GSE116073, four donors in two infection states with four treatments each. Counts were converted to counts per million on each library total, a pseudocount of 0.05 CPM was added, and a log2 ratio was taken for each of the eight pairs matched within donor and infection state. The change is 2 raised to the mean of those eight ratios and p is a two-sided paired t test on the same ratios. Benjamini-Hochberg correction was applied across the 24,957 genes reaching 0.1 CPM in either arm.

[4] Copies per cell were estimated from the normalized value (4.617 CPM on drug, 0.372 CPM in vehicle) against roughly 200,000 mRNA molecules per activated CD4+ T cell, giving <1 copy per cell on drug and 1 copy per 13 cells in vehicle. Poly(A) selection undercounts nuclear-retained long noncoding RNA, therefore the estimate is a lower bound.

Sources: GSE116073; Vautrin et al. 2019; GSE97062; Chebli et al. 2017; Scorpion Capital original analysis of the deposited counts, other analysis, modeling, estimates, and literature/publication review

ABVX repeatedly conflates inactive LINC00599 host RNAs as active mature 20 nt “miR-124” across their papers and materials. They detect inactive LINC00599 and call it “miR-124” -- they are not the same.

Conversion of LINC00599 to miR-124 is blocked. Despite Tazi’s claim, LINC00599 does not represent a “storage form”. The RT-PCR detects the 609 nt host transcript. The sponsors call it lncRNA 0599-205 or the loci encoding miR-124 in research papers but drop the qualifier in press releases, presentations, and the website. Measurement of miR-124 is simply not demonstrated – rather, measurements that cannot distinguish precursor/host RNA from mature miR-124 are presented as evidence of “miR-124” elevation.

Document and location	Term as written	Conflation or conflicting statements
Vautrin et al. 2019, Results	*“The number of reads from the three loci encoding miR-124 in the treated samples were 4- to 12-fold higher than in the untreated samples, confirming that ABX464 led to a large increase in miR-124.”*	Conflates reads in three genomic windows with active microRNA in a single sentence. Nothing in the dataset “confirms” miR-124 expression.
Vautrin et al. 2019, Results	*“All mapped reads from the miR-124-1 locus in the treated samples aligned to miR-124 and a 2 kb region surrounding it.”*	2 kb of genomic sequence is the host gene.
Vautrin et al. 2019, Results against the Figure 4D legend	*“reads that mapped to only the 85 bp miR-124 region” against “the miR-124 75 bp region”*	One form, two stated lengths in the same article obfuscates which form is measured. Both lengths are given in bp; a single-stranded transcript is measured in nt.
Manchon et al. 2020, capture sequencing	*“spliced lncRNA 0599-205 constitutes a miRNA storage form”*	The host transcript, LINC00599, is rapidly processed to miR-124 in unsilenced cells. It does not represent a “storage form” but rather a REST/PTBP1 leak.
Apolit et al. 2023, Results	*“the number of miR-124 copies was significantly higher in each treatment group than in the placebo group”*	The mature species, by droplet digital PCR, was zero. The inflated (normalized) numbers are presented in the text with units conflating the ratio with counts per cell.
ABX464-103 protocol v3.0, study objectives	*“To evaluate the effect of the different dose groups of ABX464 on miR-124 expression in tissue (RNA later) at Week 8 and Week 16”*	The probe measured all three forms and cannot distinguish them. miR-124 is stated with no confirmatory assay.
ABTECT-1 analysis plan v2.0, abbreviation list	*“miR-124 Micro-ribonucleic acid 124”*	The chemical class and the repeated index number add nothing a reader can use, and the assay measured all three forms.

[1] Across 42 documents the mature species is named 444 times and a precursor or host transcript 179 times, 173 of those inside two research papers. Our audit suggests that Abivax is measuring the sequence in the inactive host transcripts and calling it miR-124. They are not the same. One is inactive and the other active. (Counts taken 1 October 2026 from the text and figures of the posted PDFs and press release, normalized for hyphen spacing, including abbreviation lists and figure legends.)

Tazi et al. 2021 (Drug Discovery Today review) and nearly verbatim in Vautrin 2019 (Scientific Reports, with Tazi as first author):

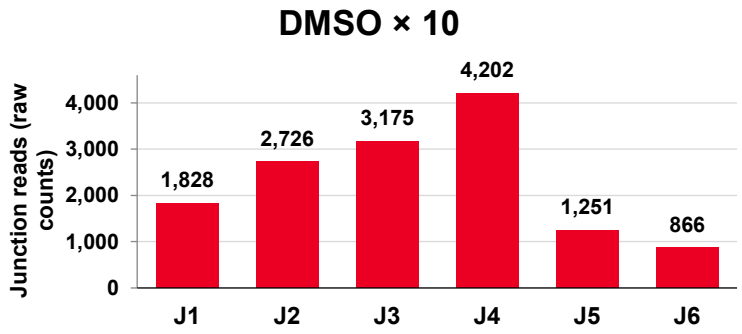
“Given that unspliced lncRNA 0599-205 will not leave the nucleus because of the quality-control machinery and the involvement of the CBC complex in this mechanism[2], spliced lncRNA 0599-255 constitutes a form of miRNA storage, possibly in addition to other functional properties of the intact spliced transcript. This storage might be maintained through low transcriptional activity and degradation of the unspliced lncRNA 0599-255 and low production of mature miR-124 under normal conditions.”

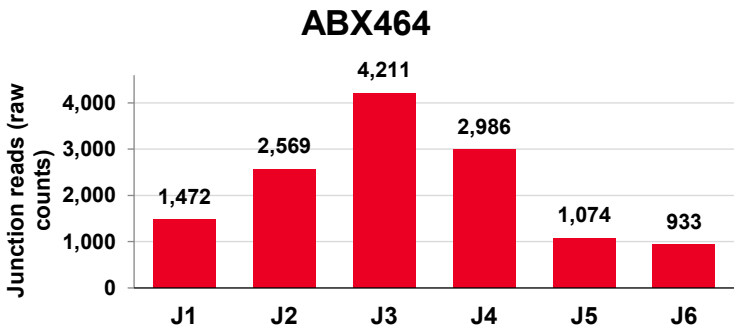
[2] We later share our original measured data showing CBC binding is an aggregation artifact. Our DLS studies confirm aggregation at assay concentrations. ABX464 has a measured aggregation threshold of 0.16 µM, so the UV-crosslinking studies are conducted well above solubility. Thus, the cross-linking study measures aggregation, not specific binding.

Sources: Vautrin et al. 2019; Manchon et al. 2020; Apolit et al. 2023; ClinicalTrials.gov NCT03760003; ClinicalTrials.gov NCT04023396; Schoenherr and Anderson 1995; Conaco et al. 2006; Lujambio et al. 2007; Morlando et al. 2008; Ballarino et al. 2009; de Rie et al. 2017; Bartel 2018; Yeom et al. 2018; Zhang et al. 2024; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The authors claim ABX464 increases splicing and thus miR-124 – but ABVX's own junction-read data show ~10× more LINC00599, not more splicing -- the spliced fraction is unchanged. More RNA ≠ more splicing.

ABVX measured junction reads within the 609-nt LINC00599 host transcript, not a downstream mature miR-124 species. The LINC00599 junction reads rise together on drug — increased host-transcript, not increased splicing. The profiles scale proportionally between groups, leaving the spliced fraction essentially identical at 15.1% on DMSO versus 15.2% on ABX464. Only the quantity rises; the splice pattern does not.





J1 to J4 are exon-intron reads (unspliced). J5 and J6 are exon-exon reads (spliced).

The figures show junction reads across LINC00599, the initial splice step that makes the 609 nt LINC00599. The leak. Manchon et al. 2020 plotted the same junction reads with the DMSO arm that Vautrin Figure 4D leaves out.[1]

ABX464 raised DMSO reads by the same multiple. The two profiles nearly overlay, so the quantity rises -- the pattern doesn't.

The two profiles differ only at J3 and J4. With those two exchanged in the DMSO arm, a single scale factor reproduces the ABX464 profile with a Pearson r of 0.99 at p < 0.001.

Test	As plotted	J3, J4 exchanged
Spliced fraction, DMSO	15.1%	15.1%
Spliced fraction, ABX464	15.2%	15.2%
Fisher exact, odds ratio (p)	1.01 (0.97)	1.01 (0.97)
Scale factor k, ABX464 = k × DMSO	9.3	9.6
Variance explained by k (R^2)	0.69	0.98
Pearson r (p)	0.84 (0.038)	0.99 (1.4e-4)
Largest junction share difference (percentage points)	9.2	1.9
Chi-square homogeneity (p)	8.7e-14	0.16

[1] Bar heights were measured by pixel from Manchon et al. 2020 Fig. 7 against its gridlines. Each arm is one pooled sample of averaged reads, so the tests compare the plotted profiles and do not estimate donor variation. Fisher and chi-square p values treat the averages as counts.

Sources: Manchon et al. 2020; Vautrin et al. 2019; Scorpion Capital analysis, modeling, estimates, and literature/publication review

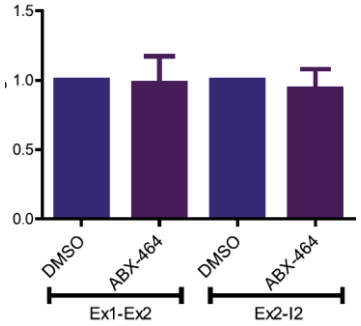
ABVX's own experiment designed to demonstrate increased splicing is negative -- ABX464 increases neither splicing nor miR-124 in HeLa cells

Vautrin 2019 states that LINC00599 splicing is required for miR-124 production; Figures 5B–C show no ABX464 effect on either step. The same negative experiment appears in three publications[1]; we found no published positive ABX464 splicing result in another cell type.

"…we failed to detect an upregulation of miR-124…in response to ABX464 treatment…"
– Vautrin, 2019

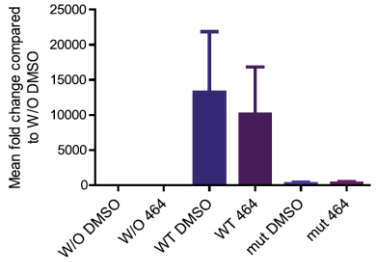
Splicing was unchanged by ABX464 (Vautrin 2019, Figure 5b)

The* sponsors *acknowledge no change in the proportion of miR-124 splice forms in HeLa cells. The graph above shows splice junction fold change unchanged, both junctions (DMSO vs ABX464).



miR-124 does not increase (Vautrin 2019, Figure 5c)

ABX464 produces no increase in the reported miR-124 signal in wild-type or splicing-mutant LINC00599 conditions. Figure legend header: "Splicing of LncRNA 0599-205 is required for the production of miR-124" -- but it doesn't change.



The experiment does not support the proposed CBC > splicing > miR-124 mechanism

The authors explain the negative result by stating that splicing is already "maximized" in HeLa cells. But this assay was explicitly designed to measure the splice junctions ABX464 is proposed to increase, and we found no published positive ABX464 splicing experiment in another cell type – the same negative experiment appears in Vautrin 2019, the Manchon 2019 preprint and Manchon 2020; we found no corresponding positive splicing dataset elsewhere in the ABVX corpus.[1]

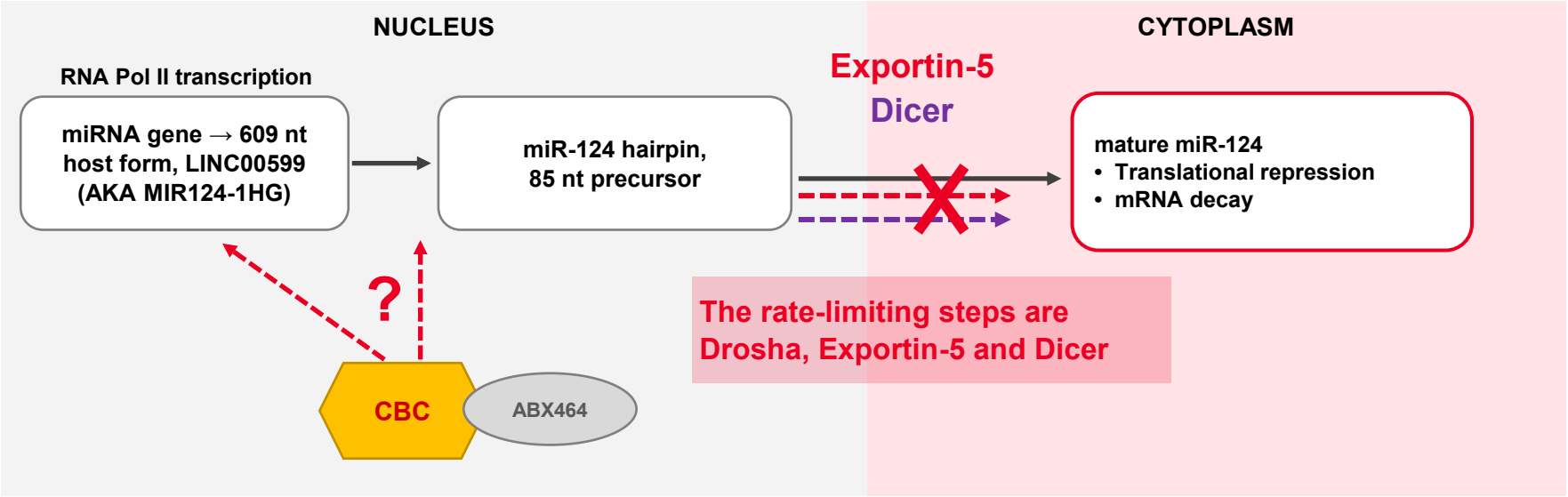
[1]The same figure appears in three publications. Scientific Reports published it in 2019 as Figure 5 under a Creative Commons Attribution license, which permits reuse when the source is credited. Manchon et al. posted it as Figure 8 in a bioRxiv preprint on 12 December 2019 and published it as Figure 8 in the American Journal of Biomedical Science and Research on 11 February 2020, six days after receipt. The 2020 article cites Vautrin et al. 2017 but does not cite the 2019 article that published the figure. No figure in it carries a permission or adapted-from line. The 2019 article declares that six of its authors are Abivax employees and that three hold Abivax stock options.

Sources: Vautrin et al. 2019; Manchon et al. 2020; Manchon et al. 2019' Scorpion Capital analysis, modeling, estimates, and literature/publication review

CBC processing is not a rate-limiting regulatory step in miR biosynthesis – as admitted in ABVX/Vautrin 2019 paper – therefore, it cannot be a modulatory step in miR-124 production, undermining the purported MOA

Vautrin 2019 itself reports no ABX464-induced miR-124 when splicing is already maximized – "…we failed to detect an upregulation of miR-124 in transfected HeLa cells in response to ABX464 treatment since splicing is maximized in HeLa cells and the CBC complex would have an effect at the site of transcription (Fig. 5B)."

The processing steps in microRNA production



Original diagram Scorpion Capital LLC

The rate-limiting steps in miRNA biogenesis are Drosha processing, nuclear export, and Dicer cleavage, not CBC. Vautrin 2019 acknowledged this bottleneck, reporting that ABX464 failed to upregulate miR-124 in WT or LINC00599-transfected HeLa cells "since splicing is maximized in HeLa cells," that is, the machinery was already saturated. Even if CBC-mediated splicing improves, it cannot bypass the bottleneck. A >1000-fold increase in mature miR-124, as claimed for clinical blood samples, cannot occur at the CBC step, consistent with the HeLa experiments Abivax presents.

Sources: Chebli et al. 2017; Vautrin et al. 2019; Bartel 2018; Gregory et al. 2004; Yi et al. 2003; Ensembl ENST00000521863; miRBase MI0000443; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Scorpion Capital recreated the Campos 2015 cross-linking buffer – our DLS data show ABX464 precipitates across the binding assay range, invalidating the key experiment used as evidence of specific CBC binding and the central pillar of the purported MOA

Dynamic light scattering (DLS, Scorpion Capital study) shows ABX464's critical aggregation concentration (solubility threshold) is <1 μM in Campos's UV cross-linking buffer. Drug bound to BSA and shifted the aggregation curve to the right. Thus, CBC will likely bind nonspecifically to drug under the assay conditions used in Campos 2015 (next slide).

METHODS (in brief)

- **DLS (Zetasizer): Z-average diameter (triplicate median) and scattered count rate vs ABX464 0 to 100 μM.**
- **Campos buffer: 20 mM Tris pH 7.5, 150 mM NaCl, 1 mM DTT, 10% glycerol.**
- **Two conditions: drug only and buffer + 1 mg/mL BSA (albumin).**
- **Quality-gated: zero / sub-1 nm / poor-intercept reads excluded; size reported as triplicate median.**

RESULTS

1. **ABX464 was a gross precipitate at every concentration we tested, no soluble phase was observed (black diamonds) in the absence of BSA.**
2. **BSA, albumin, delayed precipitate formation out to 50 μM, where aggregation began (blue triangles) (722 → 1,334 nm at 75 to 100 μM).**
3. **ABX464 appeared to bind albumin readily, shifting the apparent solubility curve right.**
4. **The precipitate settled out of solution at every concentration we tested, without BSA present.**

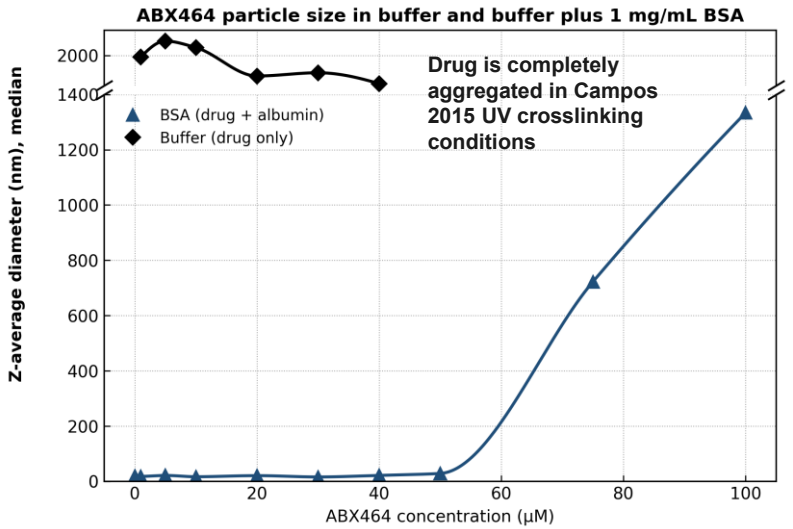


Fig 1. Z-average size vs ABX464. Without protein the drug is precipitate at every concentration (top band); albumin holds it monomeric to ~50 μM, then it aggregates.

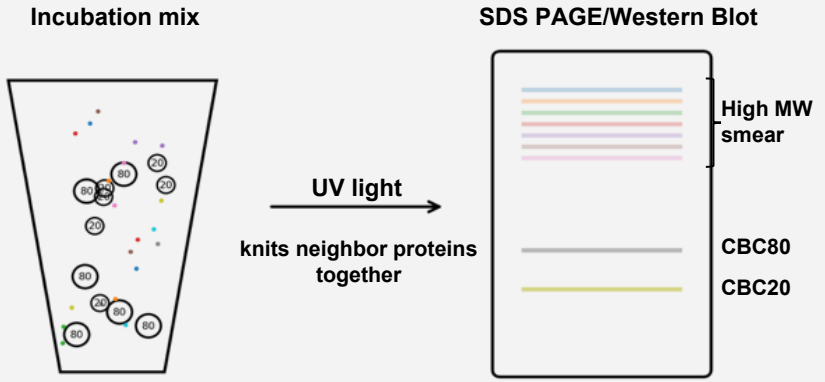
Conclusions ABX464 forms aggregates across Abivax's in-vitro working range; without protein it precipitated at every concentration tested. With albumin no aggregates were detected to ~50 μM. Therefore, the apparent solubility is protein dependent, and we could find no protein binding data presented by Abivax. These data invalidate the UV-crosslinking studies presented by Campos 2015 as proof of ABX464's modulatory CBC binding, where the only proteins in the assay were the CBC20:80 subunits.

Sources: ABX464 CAC by DLS (Scorpion Capital, 2026); companion fluorescence CAC (Protocol 4); Campos Retrovirology 2015. UV cross-linking buffer per Campos 2015; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The ABVX UV-crosslinking study -- the sole "proof" that ABX464 binds specifically to CBC – was run above the solubility limit and is an aggregation artifact. Our DLS study showed ABX464 aggregates out of solution at all concentrations ≥1 µM.

Campos irradiated ABX464 with only CBC20/CBC80 present; our DLS shows aggregation in the same buffer and concentration range. The published gels show high-MW smearing – diagnostic of an aggregation artifact in UV crosslinking studies

UV-CROSSLINKING = SOLUBILITY ARTIFACT

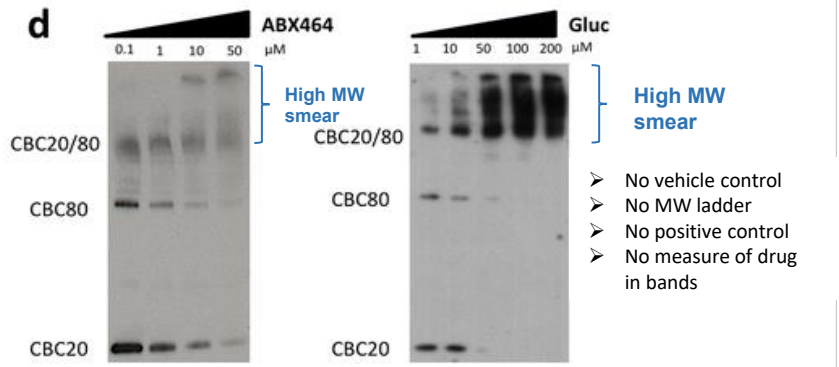


Purified CBC20, CBC80 and ABX464 were irradiated with UV light for 30 min. CBC subunits were the only proteins available to an aggregating drug above its solubility limit.

Proteins were separated on a gel by size. Antibody tags were used to visualize CBC20 and CBC80 in the bands. No controls for spontaneous dimerization (expected of a stable dimer).

High MW smears are diagnostic of an aggregation artifact in UV crosslinking studies. Our DLS study shows aggregation of ABX464 at these concentrations in the same buffer system. These are aggregation artifacts, not evidence of specific CBC binding.

Campos et al., 2015 Figure 4 d



From Campos (2015): *"Purified recombinant CBC20 and CBC80 proteins were incubated with increasing concentrations of ABX464 (left panel) or ABX464-N-glucuronide (right panel) and treated for 30 minutes with UV light. The proteins were revealed by Western Blotting using CBC20 and CBC80 antibodies." (Figure 4d).*

1. ABX464 would bind protein in the incubation mix. CBC20 and CBC80 were the proteins present; 2. Concentrations exceeded ABX464's aqueous solubility, therefore the UV pulse cross-linked nonspecific drug-protein aggregates; 3. The authors report insolubility in the same paper. ABX464 required centrifugation to remove precipitate, toxic to cell assays. They add that it bound to protein in solution.

Abivax conclusion: "obefazimod exerted an effect on …viral RNA splicing through interaction with cap-binding complex [CBC] … binding of obefazimod … stabilizes the interaction between [CBC20 and CBC80] components"

Our conclusion: ABX464 (obefazimod) aggregates completely at 1 to 50 µM (our DLS) and the bands ABVX claims are evidence of specific binding are instead drug-protein aggregates that smear the SDS-PAGE gel. The same artifact requires higher concentrations for the more polar "N-Glu" metabolite. No evidence of saturability is seen at higher concentrations, also consistent with artifact. The claim that ABX464 stabilizes the dimer is inconsistent with literature showing that the CBC complex is already a stable dimer in vivo. There is nothing for ABX464 to "stabilize".

Sources: Campos et al. 2015; Vermeire et al. 2023; Gonatopoulos-Pournatzis and Cowling 2014; McGovern et al. 2002; Feng and Shoichet 2006; Coan et al. 2009; Owen et al. 2012; Auld et al. 2017; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Chapter 16. Independent pharmacology and ABVX/Tazi's own datasets indicate obefazimod is an AhR agonist -- a core mechanism absent from ABVX's MOA narrative

Independent pharmacology and ABVX/Tazi's own datasets indicate ABX464 is an AhR agonist -- a core mechanism absent[1] from ABVX's MOA narrative

Equillium (NASDAQ: EQ) – a clinical stage biotech developing an AhR modulator for UC -- directly demonstrated ABX464 AhR reporter activation and reversal by an AhR agonist; our reanalysis of Abivax/Tazi's deposited mouse and human transcriptomes independently identifies the canonical AhR gene signature.

Part 1, ABX464 activates AhR, the proof and the consequences

The AhR gene signature is elevated in concert by ABX464. We mined the AhR signature, unreported as such, from arrays deposited by Tazi's group (Abivax). The prespecified battery (CYP1A1, CYP1A2, CYP1B1, NQO1, TIPARP, AHRR) increased significantly as a set in mouse and human transcriptome libraries.

Murine evidence Chebli 2017, bone-marrow-derived macrophages

Cyp1a1 was the top induced gene at 97× over controls in the supplemental table (FDR 9.4e-15), and 52× by our recalculation with a 0.05 CPM pseudocount.

Five of the six prespecified genes in the published tables cleared genome-wide FDR individually (Cyp1a1, Cyp1b1, Serpinb2, Tiparp, Nqo1).

Chebli published data from a single set and five others were deposited on GEO. We analyzed the six deposited pairs as a set and found the AhR battery increased 3.70-fold unstimulated and 2.59-fold stimulated (sign test p 0.0156, permutation p < 5e-5).

Human evidence Vautrin 2019, CD4+ T cells

CYP1A1 induction ranked first of 39,599 genes in HIV-infected cells and second of 39,767 in uninfected cells.

The battery was co-induced in 6 of 6 genes (competitive p 1.6e-4, permutation p < 5e-5, sign test p 0.0156).

Reversibility. **Equillium is developing a transient AhR agonist, EQ504, for therapeutic use and used ABX464 as a comparator. ABX464's elevation of CYP1A1 RNA and IL-10 cytokine was reversed by the AhR antagonist GNF-351, providing pharmacological proof that ABX464 activated AhR.**

The binding pocket. **Equillium showed ABX464 docked into the AhR PAS-B pocket in the cryo-EM structure PDB 7ZUB, with indirubin as the bound ligand. These data place ABX464 inside the AhR binding pocket.**

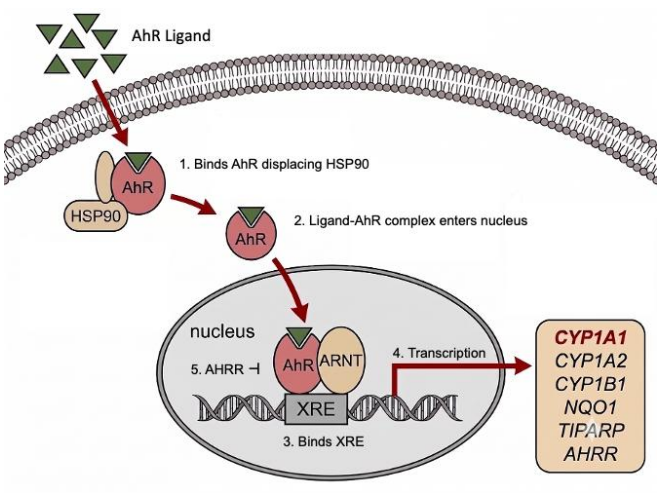
The consequence. **A compound with ABX464's physical properties and reported PK is predicted to chronically activate AhR. Under chronic activation AhR promotes the three steps of carcinogenic transformation, including boundary escape, which would push precancers and occult lesions to full malignancies.**

[1]Absent per the following search methodologykeywords/terms: literal text search over deduplicated machine-readable extracts of 34 Abivax conference and corporate documents (351,413 characters) and 13 primary Abivax and Tazi papers with supplements (570,709 characters), for: aryl hydrocarbon, AhR, CYP1A1, CYP1A2, CYP1B1, NQO1, TIPARP, AHRR, XRE, xenobiotic response element, dioxin. AhR appears twice. On the Special Call of 1 June 2026 Abivax named AhR agonists as an orthogonal mechanism to combine with obefazimod, and in the primary papers the receptor is named in a reference title citing another group. CYP1A2 appears in the ABX464-102 and ABX464-104 protocols as a concomitant-medication restriction. No occurrence describes obefazimod as acting through AhR.

Sources: Chebli et al. 2017; Vautrin et al. 2019; Equillium 2026; Gruszczyk et al. 2022; Scorpion Capital reanalysis, modeling, estimates, and literature/publication review

Why AhR matters: transient activation supports gut homeostasis, but persistent activation and chronic signaling promotes tumors

AhR is a xenobiotic sensor whose biology depends heavily on duration: rapidly cleared ligands produce a physiological pulse, while persistent exposure can sustain CYP induction and pathologic signaling.



AhR defined

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor and the body's sensor for environmental toxins. In the cytoplasm it is bound to HSP90 and XAP2, which hold it inactive. Its signature output is gene transcription, but it also has direct protein-protein interactions (IL-22 is modulated both ways).

HISTORY

AhR was discovered as a dioxin signal. In 1976 Poland and colleagues identified a high-affinity binding protein for TCDD in liver cytosol. For two decades it was studied as a mediator of dioxin toxicity. Later work established its physiological role in gut immunity, barrier maintenance, Th17/Treg balance, and M1/M2 polarization. Transient activation is driven by microbial tryptophan metabolites and dietary indoles. AhR maintains gut function in addition to its detoxification role. The beneficial role requires transient stimulation. Chronic stimulation is carcinogenic.

AhR signal transduction, the coordinated steps of transient AhR activation

1. **Ligand binds cytoplasmic AhR, initiating its nuclear localization signal.**
2. **The complex translocates to the nucleus and binds ARNT.**
3. **ARNT-AhR-ligand complex binds the XRE (xenobiotic response element) on DNA for gene induction.**
4. **The canonical gene battery is transcribed: CYP1A1, CYP1A2, CYP1B1, NQO1, TIPARP and AHRR. (This is the induction signature we found in the mouse and human transcriptomes described next.) The enzymes metabolize the transient ligand. Ligands that are poor substrates (TCDD) persist.**
5. **AHRR and TIPARP feed back to turn off AhR.**

TRANSIENT AGAINST CHRONIC AhR ACTIVATION

Transient ligands are metabolized, have short half-lives and clear rapidly, limiting the signal to a pulse. FICZ, the prototypic transient AhR ligand, is a substrate for the CYP1A1, CYP1A2 and CYP1B1 enzymes it induces; its signal is a pulse. AHRR and TIPARP repress the receptor after ligand metabolism completes. TCDD is the prototypic chronic AhR ligand and a known carcinogen, with a human elimination half-life of years, so the receptor is chronically active. CYP1A1 remains elevated, and bioactivation runs continuously. Carcinogenic ROS intermediates form. Our research and analysis leads us to conclude that ABX464 will produce a chronic AhR signal with QD dosing and a logP of 6.35 (Scorpion Capital, measured logP).

Sources: Poland et al. 1976; Gruszczyk et al. 2022; Rannug 2022; NTP Report on Carcinogens; Scorpion Capital reanalysis, modeling, estimates, and literature/publication review

Abivax/Tazi's own deposited mouse data reveal coordinated AhR activation -- all six prespecified AhR genes rise with ABX464

Our reanalysis of GEO GSE97062 finds the six-gene AhR signature significantly elevated in both unstimulated and LPS-treated macrophages. Chebli published only one culture pair of six and did not identify the pattern as AhR activation. ABX464 also induced IL-22 in mouse bone-marrow-derived macrophages. Abivax attributes this IL-22 induction to miR-124, yet IL-22 is a well-established AhR-regulated cytokine; taken together with the coordinated AhR gene signature, the data indicate that ABX464 drives IL-22 in concert with AhR activation..

The AhR battery increased in the six deposited culture pairs, including the single pair that Chebli chose to publish, the pair with the highest IL-22 fold-change, an outlier among the datasets.

Mouse bone-marrow-derived macrophages, GEO GSE97062. Fold-change against the vehicle culture from the same biological group.

Gene	Chebli, no LPS one selected culture pair (fold increase)	Our analysis, no LPS all six culture pairs (fold increase)	Our analysis, LPS all six culture pairs (fold increase)
IL-22	*not reported*	2.33×	6.81×
Cyp1a1	97×	27.68× †	7.49× †
Cyp1b1	3.16×	3.39×	3.13×
Serpinb2	3.11×	3.33×	2.16×
Tiparp	2.33×	2.14×	1.65×
Ahrr	*not reported*	2.00×	1.81×
Nqo1	*not reported*	2.13×	2.07×
Set fold change	*not reported*	3.70×	2.59×
Members elevated	*not reported*	6 of 6	6 of 6
Sign test p	*not reported*	0.0156	0.0156
Permutation p	*not reported*	< 0.00005	< 0.00005

The prespecified six-gene AhR induction set: Cyp1a1, Cyp1b1, Tiparp, Ahrr, Nqo1 and Serpinb2 increased significantly as a set with ABX464 treatment.

Chebli reported only one culture pair of six for each condition, the pair with the highest IL-22 induction, an outlier lying well above the IL-22 induction levels in the other pairs. The exclusion threshold of ≥2-fold excluded Ahrr from both supplementary tables and Nqo1 from the no-LPS table (Supplementary Tables S3 and S4). We used the raw counts from the twenty-four sample files on GEO in our analyses (GSE97062).

Our set-level test compared the mean count paired log2 ratio of the six genes against 20,000 random six-gene sets drawn from an expression-rank-matched window. † Cyp1a1 mean vehicle counts were 2.3 at baseline, at the limit of detection, which would artificially magnify the fold-change (we used a standard 0.05 CPM pseudocount to eliminate this artifact). The pseudocount corrected the 191-fold IL-22 induction claimed to 42-fold.

Sources: Chebli et al. 2017; GSE97062; Scorpion Capital reanalysis, modeling, estimates, and literature/publication review

Another extraordinary signal: ABVX/Tazi's deposited human T-cell data independently confirm AhR activation -- CYP1A1 is the #1 induced gene in both conditions

In GSE116073, ABX464 significantly induces the prespecified AhR gene set in both infected and uninfected human CD4 T cells; CYP1A1 ranks first genome-wide in both -- human-cell confirmation of the same pathway seen in mouse. ABVX only discusses AhR agonists as potential combination therapies[1]. We note that pairing two AhR agonists would be less than additive.

The data are a prespecified XRE-core set {CYP1A1, CYP1A2, CYP1B1, NQO1, TIPARP, AHRR}; competitive rank test (set vs genome) plus a 20,000-permutation null, directional UP. GSE116073 original Scorpion re-analysis.

Fold activation (ABX464/vehicle) of AhR gene-set in human CD4 T-cells (infected and uninfected)[2]

Gene	Uninfected	HIV-1 infected
AhR battery, prespecified six		
CYP1A1	9.93×	14.39×
CYP1B1	3.65×	2.40×
CYP1A2	3.03× †	1.63× †
TIPARP	1.52×	1.73×
AHRR	1.62×	1.55×
NQO1	1.11×	1.06×
Receptor, partner and the NRF2 arm, no change expected		
AHR	1.06×	0.98×
ARNT	1.11×	1.07×
NFE2L2	1.23×	1.07×

†fewer than 100 counts in each sample

ABX464 significantly elevated the prespecified six-gene AhR gene-set

Contrast	AhR-set mean log2FC	Competitive p	CYP1A1 genome rank
C1 ABX464 vs DMSO	+1.62	1.6e-4 (perm 5e-5)	#1 / 40,475
C5 ABX464 vs darunavir	+1.25	2.2e-4	#1
C3 darunavir vs DMSO	+0.37	0.102 / 0.116	#7,534
C4 N-Glu vs DMSO*	+1.27	1.2e-4	#4

**We believe the N-Glu activity is artifactual. N-Glu was partially active relative to ABX464, but it does not fit in the binding pocket and does not activate AhR in the reporter assay, so this is likely artifact of regenerated parent during the 6-day incubation and not a direct effect of N-Glu on AhR. (Enzymes that cleave glucuronides are ubiquitous and expected in T cell lysates.)*

Tazi's group deposited the human cell transcriptomes without naming AhR even though the flagship AhR signal, CYP1A1, was the number 1 hit in a library comprising 40,475 total genes. The sponsors do not discuss AhR activity in this context[1]. We find this omission inexcusable, since ABX464's physical characteristics place it squarely in the chronic AhR TCDD Class, mostly composed of Group 1 carcinogens.

[1]Disclosure search. Literal text search over deduplicated machine-readable extracts of 34 Abivax conference and corporate documents (351,413 characters) and 13 primary Abivax and Tazi papers with supplements (570,709 characters), for: aryl hydrocarbon, AhR, CYP1A1, CYP1A2, CYP1B1, NQO1, TIPARP, AHRR, XRE, xenobiotic response element, dioxin. AhR appears twice. On the Special Call of 1 June 2026 Abivax named AhR agonists as an orthogonal mechanism to combine with obefazimod, and in the primary papers the receptor is named in a reference title citing another group. CYP1A2 appears in the ABX464-102 and ABX464-104 protocols as a concomitant-medication restriction. No occurrence describes obefazimod as acting through AhR.

[2]Per-gene fold changes are median against the DMSO vehicle culture from the same donor and infection state, four pairs per comparison, reported as descriptive. † marks a result carried on fewer than 100 counts in every sample. Method note: the competitive test is a rank-based set-versus-genome comparison (Mann-Whitney, directional), corroborated by a 20,000-permutation null and cross-checked with limma::camera, which adds inter-gene correlation correction. Reanalysis by Scorpion Capital LLC.

Source: GSE116073 (Vautrin et al. 2019), Scorpion Capital re-analysis of deposited raw counts, modeling, estimates, and literature/publication review

Third-party Equillium places ABX464 directly in the canonical AhR ligand pocket -- the same pocket occupied by the endogenous ligand indirubin

Using the experimentally solved AhR PAS-B structure (PDB 7ZUB), Equillium modeled ABX464 in the conserved ligand-binding pocket -- N-Glu did not fit.

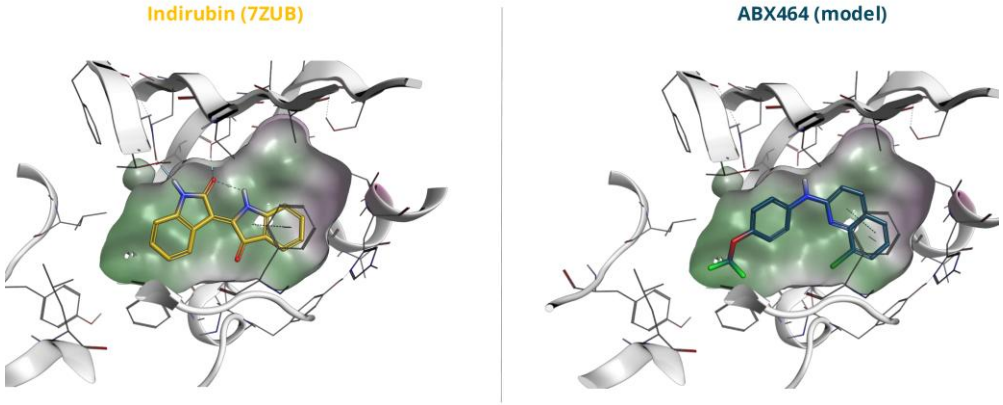


Figure reproduced from Equillium Inc., Insights into the Aryl Hydrocarbon Receptor and miR-124 Axis, S. Connelly, webinar 27 May 2026, slide 13. PDB 7ZUB from Gruszczyk et al., Nat. Commun. 2022. Figure generated using MOE 2024.0601.

THE POCKET

AhR's ligand site is the PAS-B domain. Equillium describes it as a large hydrophobic binding cleft that accommodates a diverse range of ligands: endogenous indoles and tryptophan derivatives, dietary flavonoids and polyphenols, and xenobiotics including halogenated and polycyclic aromatic hydrocarbons.

METHODS

Induced-fit docking was modeled against the experimentally solved structure PDB 7ZUB (Gruszczyk et al., Nat Commun 2022), with the pocket allowed to adapt. Positions were ranked by S-score and filtered on aromatic orientation, pocket complementarity and steric clashes. MOE 2024.0601, Triangle Matcher placement, London dG scoring, GBVI/WSA dG rescoring.

RESULTS

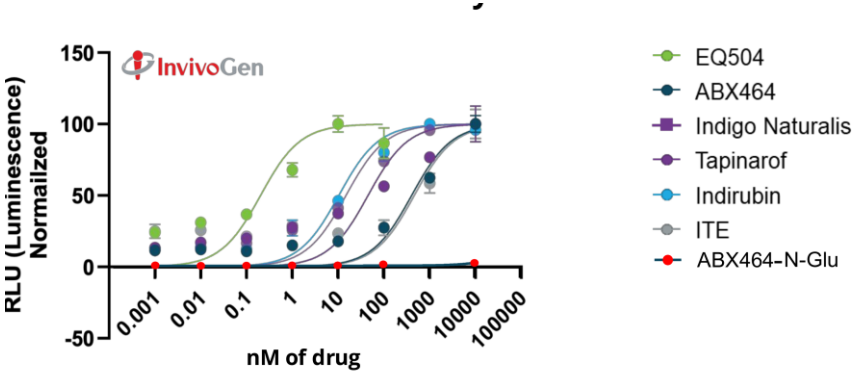
Equillium's caption, verbatim: "ABX464 docks into the lipophilic PAS-B pocket leveraging conserved π-π stacking with key residue Phe295." Indirubin, the bound ligand in 7ZUB, anchors through a conserved indole π-π stack, and ABX464's quinoline takes the same position. Glucuronidation introduces polar steric bulk and disrupts planarity. The N-glucuronide did not fit.

Sources: Equillium 2026; Gruszczyk et al. 2022; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Equillium directly measured ABX464 as an AhR agonist. At ABVX's favored, published 5 µM assay concentration, AhR activation was near-maximal (92%) – yet ABVX attributes the signal to miR-124 elevation rather than AhR.

This is direct AhR-reporter pharmacology, not an inference from downstream gene expression: ABX464 produces near-maximal receptor activation at 5 µM, while N-Glu is inactive.

Dose-response curves and EC50 values for a panel of AhR agonists, as shown in the referenced Equillium presentation. ABX464 was active.



Compound	EC50 (nM)
EQ504	0.203
Indirubin	10.39
Indigo Naturalis	14.89
Tapinarof	45.21
ABX464	404.2
ITE	461.8
ABX464-N-Glu	not detectable

Figure reproduced from Equillium Inc., webinar 27 May 2026, slide 17. HepG2-Lucia AhR reporter cells (InvivoGen). Four-parameter fit, smallest and largest values were fixed to 0 and 100.

ABX464 activates AhR, the metrics

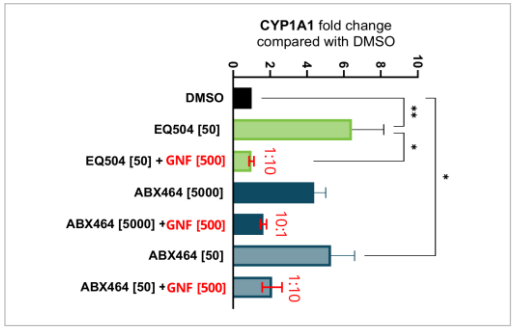
ABX464 (µM)	Normalized RLU % activation	Source
1	63%	Measured point
5	92%	Read off the curve
10	99.9%	Measured point

- Equillium curve-fit with a four-parameter model setting the smallest and largest values to respective 0 and 100.
- Concentrations were 0.001 to 10,000 nM.
- ABX464 had an EC50 of 0.4 µM and N-Glu was inactive.
- The 5 µM concentration is used in both deposited transcriptome experiments and other cellular assays.
- Abivax attributes the observed effects to miR-124.
- We note that the ABX464 assays were conducted at near-maximal AhR activation.

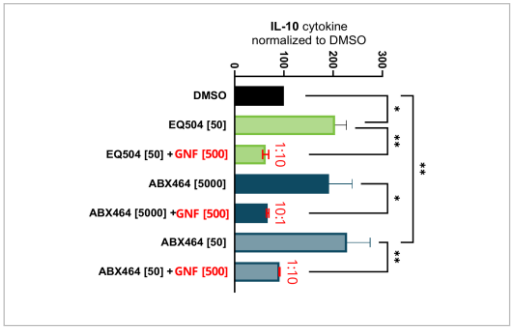
Sources: Equillium 2026, slide 17; Scorpion Capital digitization; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Equillium then blocked ABX464's effects with an AhR antagonist -- pharmacological proof that ABX464 activates AhR. ABX464 increased CYP1A1 and IL-10, and the AhR antagonist (GNF-351) blocked both readouts, providing clear confirmation of AhR-mediated activity.

CYP1A1 induction



IL-10 protein



Black bar = DMSO control

Green bars = EQ504 (Equillium's AhR agonist)

Dark blue bars = ABX464, 5 μM

Light blue bars = ABX464, 0.05 μm

EQ504 and ABX464 elevated both CYP1A1 (~4 to 6-fold) and IL-10 (about 2-fold).

AhR antagonist GNF-351 reversed both.

Both panels: naive CD4 T cells differentiated into regulatory T cells (standard Treg cocktail, low CD3/CD28, 7 days), blocked with GNF-351 at 0.5 μM for one hour before drug. Four donors. Not PBMC. Data are as published, including the EQ504 arms.

Arm	Concentration (μM)	CYP1A1, fold vs DMSO (error bar)	IL-10, % of DMSO (error bar)
DMSO	NA	1.0	100
ABX464	5	4.4 (1.2)	191 (94)
ABX464 + GNF-351	5 + 0.5	1.6 (0.4)	67 (8)
ABX464	0.05	5.3 (2.5)	228 (93)
ABX464 + GNF-351	0.05 + 0.5	2.1 (1.2)	91 (5)

1. Table bar values read from the published figure by pixel calibration against its printed axis ticks. Equillium published no numeric table; we derived it from the figure. DMSO is the normalization reference on each panel.
2. Equillium does not state whether the error bars are SD or SEM.
3. Significance marks are Equillium's as printed. Their legend reads ****p<0.00001, ***p<0.0001, **p<0.001, *p<0.005 versus DMSO by ordinary one-way ANOVA, while the brackets connect treatment pairs by an un-named multiple comparison test.

Sources: Equillium 2026, slides 29 and 30; Scorpion Capital digitization; Scorpion Capital analysis, modeling, estimates, and literature/publication review

A key driver of carcinogenicity is duration: AhR can be beneficial as a pulse but dangerous as a chronic signal — ABX464's PK exhibits the potential to turn a transient pathway into sustained AhR signaling.

FICZ -- the prototypical transient AhR ligand -- is rapidly cleared and terminates the AhR signal, while ABX464 persists for weeks, creating the potential for sustained AhR activation.

	FICZ, a transient ligand	ABX464, a chronic ligand
Category	Endogenous tryptophan photoproduct, the prototypic physiological AhR ligand	Daily oral drug, taken for ulcerative colitis maintenance.
logP	4.3, computed (PubChem CID 1863). Cleared by the enzymes, no tissue retention	6.35, measured (Scorpion Capital, logP and pKa, 2026). 2.2-million to 1 preference for tissues, highly retained
Elimination half-life	About 14 minutes[1], not retained in tissues.	N-glucuronide 4.2 days (Scherrer et al. 2017). The metabolite and parent are interchangeable drug forms by enterohepatic recirculation.
Cleared by the enzymes it induces	Yes. FICZ is a substrate for CYP1A1, CYP1A2 and CYP1B1	Abivax has not disclosed the metabolic pathway formally. The Campos 2015 supplement suggests reactive intermediates form in addition to N-Glu in some species, but the data are in non-induced liver cells.
AHRR termination	Completes. The signal is a pulse.	Overwhelmed by chronic signal. We believe the pathway is carcinogenic, per the analysis/data in this report.
Receptor exposure	Transient.	Chronic.
Precedent class	Physiological AhR signaling. Beneficial barrier repair and gut homeostasis.	TCDD class lipophiles (TCDD half-life in humans is 5.8 to 11.3 years), which are a Group 1 carcinogen[2]

TRANSIENT AhR PULSE –
BARRIER FUNCTION AND REPAIR.

1. Increased: IL-10 and IL-22
2. Decreased: IL-6
3. CYP1/UGT enzymes clear the ligand
4. AHRR shuts off the signal and the cell replenishes energy and anti-oxidant pools.

CHRONIC SIGNAL –
CANCER TRANSFORMING STEP VIA AhR PATHWAY L

- Initiation, CYP1A1 and CYP1B1 generate reactive epoxides faster than conjugation can handle. The cell loses energy stores and antioxidants.
- Promotion, AhR drives proliferation, with apoptosis and DNA repair suppressed, and depleted antioxidants amplifying DNA damage.
- Progression, release of contact inhibition; MMP-1 and MMP-9 degrade the basement membrane, and expanded regulatory T cells (permissive) and IDO remove immune constraint. IDO generates kynurenine, which also stimulates AhR in a positive feedback loop.

[1]The FICZ half-life is derived, not published. Hajizadeh et al. (2025) dosed male Sprague-Dawley rats intraperitoneally and measured tissue FICZ. At 127.9 µg/kg, liver FICZ was 484.01 nM at 1 hour and 23.15 nM at 2 hours. Taking first-order decay across that interval, k = ln(484.01/23.15)/60 min = 0.0507 per minute and t½ = 0.693/0.0507 = 13.7 minutes. With only 2 timepoints, it is an interval estimate rather than a terminal half-life. The authors report no half-life, their 5- and 10-minute serum reads fell below instrument sensitivity. Our calculations provide a comparator for TCDD persistence only.

[2]IARC places agents in four categories: Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; and Group 3, not classifiable as to its carcinogenicity to humans. Group 1 is the highest. It applies on sufficient evidence of carcinogenicity in humans, or on sufficient evidence in experimental animals together with strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens. TCDD was the first agent placed there by the second route, on the strength of the aryl hydrocarbon receptor mechanism. IARC identifies hazard and does not quantify risk at a given exposure.

Sources: Hajizadeh et al. 2025; Campos et al. 2015; Scherrer et al. 2017; Rannug 2022; PubChem CID 1863; Peng et al. 2009; Ishida et al. 2010; IARC Monographs Volume 100F; IARC Preamble 2019; NTP Report on Carcinogens; Scorpion Capital logP and pKa lab experiments, 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The danger from sustained AhR activation – a framework that may explain the Phase 3 findings: the pathway participates in initiation, tumor promotion and progression, including escape from tissue and immune restraints

Persistent AhR signaling can engage multiple recognized carcinogenic processes simultaneously: reactive-metabolite formation, cell-cycle signaling, loss of contact restraint, matrix degradation, apoptosis suppression and immune evasion.

INITIATION

CYP1A1 and CYP1B1 generate reactive epoxides, diol-epoxides and catechol-estrogen quinones that damage DNA, while AhR represses nucleotide excision repair (Pollet et al. 2018).

PROMOTION

The AhR complex with CDK4 and cyclin D1 drives cell-cycle entry (Barhoover et al. 2010), and loss of gap junction intercellular communication removes the restraint neighboring cells normally impose (Baker et al. 1995).

PROGRESSION

MMP-1 and MMP-9 are induced and degrade the basement membrane allowing transformed cells to migrate through (Peng et al. 2009). Boundary escape is the first step in cancer metastasis.

WHAT CHANGES	EFFECT OF CHRONIC AhR ACTIVATION
Gap junctions uncoupled	Neighboring cells exchange restraint signals through gap junctions. AhR agonists uncouple them by depleting connexin proteins (Baker et al. 1995).
Contact inhibition released	AhR is nuclear and transcriptionally active in sparse cultures and is exported to the cytoplasm as cells reach confluence in culture (Ikuta et al. 2004). Holding AhR in the nucleus overrides confluence.
Cell-cycle entry driven	AhR complexes with CDK4 and cyclin D1 (Barhoover et al. 2010), deregulating contact inhibition via JunD and cyclin A (Weiss et al. 2008).
Basement membrane and matrix degraded	AhR induces MMPs, enzymes that degrade the matrix that contain tissue compartments and precancers (Peng et al. 2009).
Apoptosis suppressed in the cells that escape	Chronic AhR activation suppresses apoptosis in vivo, the damaged cell fail-safe. In experimental systems this tumor promotion pathway is the leading contributor to clonal expansion of altered hepatic foci.
Immune surveillance suppressed	AhR expands regulatory T cells and suppresses effector responses, and induces IDO, whose product kynurenine is itself an AhR ligand, an autocrine tolerance loop allowing cancer cells to evade immune surveillance (Quintana et al. 2008).

THE CUMULATIVE CONSEQUENCE OF CHRONIC AhR SIGNALING – PROMOTION OF CARCINOGENESIS

Most adults carry initiated clones and microscopic neoplasia that remain clinically silent, held in check by an intact basement membrane and immune surveillance. Chronic AhR activation removes both while simultaneously generating reactive metabolites that initiate DNA mutations and new precancerous clones. Without boundary escape an occult cancer may remain undiagnosed throughout a lifetime (Murray et al. 2014). Applying chronic AhR to an adult patient as a chronic therapy could allow controlled hyperplasias to transform into cancer and push occult cancers into symptomatic masses. We believe this framework may explain the Phase 3 findings discussed later.

Sources: Baker et al. 1995; Ikuta et al. 2004; Quintana et al. 2008; Weiss et al. 2008; Peng et al. 2009; Barhoover et al. 2010; Murray et al. 2014; Pollet et al. 2018; Scorpion Capital AhR analysis/report, 2026, Box 4; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Chapter 17: Obefazimod's lipophilicity + AhR activation converge on a disturbing potential mechanism for cancer promotion

Independent cancer literature links both sides of our hypothesis to tumor biology: chronic AhR signaling can promote tumor progression, while LDLR-high cancer cells increase lipoprotein uptake and can selectively accumulate lipoprotein-associated drugs. ABX464 combines both properties — AhR agonism and extreme lipophilicity — making this a plausible mechanistic framework, not a proven ABX464-specific pathway.

These publications establish the individual biological components; none studied ABX464. Our hypothesis is that ABX464's independently demonstrated AhR agonism and extreme lipophilicity could place it at the intersection of these pathways

Aryl hydrocarbon receptor ligands in cancer: friend and foe

This review states that AHR influences initiation, promotion, progression and metastasis, and notes increased AHR and constitutive nuclear localization in aggressive tumors, consistent with chronic AHR activation facilitating tumor progression.

The aryl hydrocarbon receptor repressor is a putative tumor suppressor gene in multiple human cancers

Zudaire et al. found AHRR downregulated by hypermethylation across multiple cancers; reducing AHRR increased anchorage-independent growth, resistance to apoptosis, invasion, angiogenesis and tumor growth. Importantly, they also observed partial AHRR loss in nonmalignant colon polyps.

Circulating Lipoproteins: A Trojan Horse Guiding Squalenoylated Drugs to LDL-Accumulating Cancer Cells

The investigators deliberately used circulating lipoproteins to carry a lipophilic drug into LDL-accumulating cancer cells, exploiting tumor LDL uptake as a delivery route.

Reconstitution of Low-Density Lipoproteins with Fatty Acids for the Targeted Delivery of Drugs into Cancer Cells

The abstract explicitly states that LDL can target drugs to cancer cells that overexpress LDLR.

Source: https://pubmed.ncbi.nlm.nih.gov/25568920/; https://pubmed.ncbi.nlm.nih.gov/18172554/; https://pubmed.ncbi.nlm.nih.gov/28606375/; https://pubmed.ncbi.nlm.nih.gov/28646542/

17 malignancies have been reported across Phase 2 and Phase 3, by our count – of these, 16 occurred on active drug and 13 at 50 mg, the highest clinical dose

The distribution of malignancies is notable: 16 of 17 occurred on active drug and 13 occurred at 50 mg. Several appeared within the first year of exposure, and Abivax itself assessed multiple non-melanoma skin cancers as possibly or probably treatment-related. The remainder of this chapter examines whether ABX464's independently demonstrated AhR agonism and extreme lipophilicity provide a biologically plausible framework for this clinical signal.

Cancer	Study and phase	Dose	Age (years)	Exposure (months)	Abivax causality
Malignancies (excluding NMSC)					
Malignant meningioma, Grade III	Phase 2, ABX464-104	50 mg	65+	14.0	Not related
Prostate, Stage I, Grade Group 2	Phase 3 induction, ABX464-105	50 mg	60+	0.5	Not related
Breast	Phase 3 maintenance Part 1, ABX464-107	50 mg	65+	6.8	Unlikely related
Prostate	Phase 3 maintenance Part 1, ABX464-107	50 mg	50+	8.5	Unlikely related
Myeloproliferative neoplasm	Phase 3 maintenance Part 2, ABX464-107	50 mg	40+	7.4	Not related
Prostate, Gleason 7B, cT2 N0 M0	Phase 3 maintenance Part 2, ABX464-107	50 mg	55+	3.4	Not related
Non-melanoma skin cancers (NMSC)					
Squamous Cell Carcinoma	Phase 2, ABX464-103/104/108	50 mg	55+	28.9	Unlikely related
Basal Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	Placebo	70+	1.9	Not related
Squamous Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	25 mg	60+	8.7	Not related
Basal Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	50 mg	70+	6.1	Unlikely related
Basal Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	50 mg	45+	5.5	Not related
Squamous Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	50 mg	70+	3.5	Possibly related
Squamous Cell Carcinoma	Phase 3 maintenance Part 1, ABX464-107	50 mg	60+	2.8	Possibly related
Basal Cell Carcinoma	Phase 3 maintenance Part 2, ABX464-107	25 mg	50+	8.1	Unlikely related
Squamous Cell Carcinoma	Phase 3 maintenance Part 2, ABX464-107	25 mg	75+	8.3	Probably related
Basal Cell Carcinoma	Phase 3 maintenance Part 2, ABX464-107	50 mg	40+	10.4	Probably related
Squamous Cell Carcinoma	Phase 3 maintenance Part 2, ABX464-107	50 mg	55+	4.6	Not related

Sources/notes: Abivax Part 2 readout webcast deck, June 2026; Abivax investor presentation, 29 June 2026; Abivax corporate presentation, 1 June 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review; case counts are descriptive and do not adjust for treatment-arm size or exposure duration

ABX464's extreme lipophilicity would predict, in our view, that most circulating parent drug may associate with lipoproteins -- potentially concentrating exposure in receptor-rich tumors, precancers and metabolically active tissues. Premalignant cells may create a perfect storm -- increased lipoprotein uptake, AhR signaling, and loss of AHRR feedback could concentrate drug in cells where AhR feedback is already impaired.

The tissues with Phase 3 malignancies (skin, prostate, breast, marrow) express high LDL receptor (LDLR) and scavenger receptor class B type 1 (SR-B1). One colonic dysplasia was also reported. Both receptors can provide uptake routes for lipoprotein-associated drug

ABX464 is uncharged in the body, with a measured logP of 6.35, a lipid-water preference of 2.2 million to one. Our audit estimates 98% of blood-borne parent drug may be in lipoproteins.[1] Lipoprotein will concentrate a logP 6.35 drug 200 to 250-fold against bulk plasma, assuming a lipid phase 0.4 to 0.5% of plasma volume.[2] Lipoprotein uptake scales with receptor density. A neutral drug with logP 6.35 would be expected to partition strongly into circulating lipoproteins without an engineered carrier..

Lipoproteins transport cholesterol and fat in blood, since neither dissolves in water.

1. **VLDL (very low density) delivers triglyceride to heart, muscle and fat. Lipoprotein lipase (LPL), anchored on the capillary endothelium of heart, skeletal muscle and adipose, strips the triglyceride in place. The free fatty acids cross into the tissue via fatty acid transport proteins. Surface-associated drug can transfer to the tissue during lipolysis, while core-partitioned drug stays with the remnant.**
2. **LDL (low density) delivers cholesterol to cells expressing the LDL receptor.**
3. **HDL (high density) is taken up through SR-B1 in liver, adrenal and prostate. SR-B1 strips the core lipid and releases the depleted particle, while the LDL receptor internalizes the whole particle with any associated drug. Tumors upregulate both receptors to feed rapid membrane synthesis.**

Pancreatic beta cells carry LDLR, VLDLR, CD36 and SR-B1, and the islets are among the best-perfused tissue in the body. After a high fat meal the drug may be delivered in chylomicrons via intestinal lymphatics. ABX464 has a large food effect supporting this mechanism.

Heart and skeletal muscle also take up lipoproteins. Fatty acids supply about 70% of cardiac ATP. Abivax increased cardiac monitoring in the Phase 3 trials and restricted inclusion for patients with cardiac risk.

1. Partition balance, $f = K\varphi / (1 + K\varphi)$, with $K = 10^4$ and $\varphi = 0.004$ to 0.005, giving $f = 98\%$. K is set 2.35 orders of magnitude below the measured logP, which lowers the estimated bound fraction.
2. Enrichment $E = 1 / \varphi$, with φ the lipoprotein lipid volume fraction of plasma taken as 0.004 to 0.005.
3. Versluis is a mouse B16 melanoma model using apoE-enriched liposomes, not ABX464.
4. Plasma Cmax 15 ng/mL fasted and 40 ng/mL fed at 50 mg, converted at molecular weight 339.
5. TC50 from the Campos Figure 1c regression on LC-MS/MS measured concentrations, 19.4% of nominal.

Sources: Lipoproteins and cancer (EBioMedicine review); Cholesterol-induced mammary tumorigenesis and LDLR upregulation; Kruit et al. 2010; Perego et al. (beta-cell receptor complement); Versluis et al. 1998; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Lipoprotein transport is an established tumor-delivery strategy. Cancer researchers have leveraged lipoprotein receptor over-expression to selectively deliver chemotherapeutic drugs to tumors -- ABX464 could access the same tumor-targeting route without any engineered carrier, as extreme lipophilicity is already akin to a drug-delivery technology.

Lipoproteins "*have been described as excellent carriers for targeted delivery of various drugs and imaging agents, due to their endogenous, long-circulating nature and to their ability to be recognized and taken up via the LP receptors*" (Sobot et al. 2017). Tumor cells upregulate the LDL receptor to meet cholesterol demand, therefore a drug associated with a lipoprotein carrier is delivered to the tumors expressing lipoprotein receptors.

Study	Drug and carrier	Model	Result
Vitols 1990	A water-insoluble alkylating agent incorporated into LDL at about 1,500 molecules per particle	Mouse leukemia, with LDL-receptor-negative mutant cells as the control	LDL-receptor dependence demonstrated against the receptor-negative control. Median survival prolonged 2.5-fold
Versluis 1998	A lipophilic daunorubicin derivative in apoE-enriched liposomes	B16 melanoma in mice	Tumor uptake ranked behind adrenals, liver and spleen, the tissues with the highest lipoprotein receptor expression
Sobot 2017	Squalene-conjugated gemcitabine. No targeting ligand and no formulation step: it loads onto endogenous LDL on its own	MDA-MB-231 (LDL receptor high) against MCF-7 (LDL receptor low) xenografts	LDL carried 37% of the drug in human plasma at 43 molecules per particle, with 500-fold higher affinity than albumin. Tumor uptake ran 2-fold higher in the LDL receptor high tumor

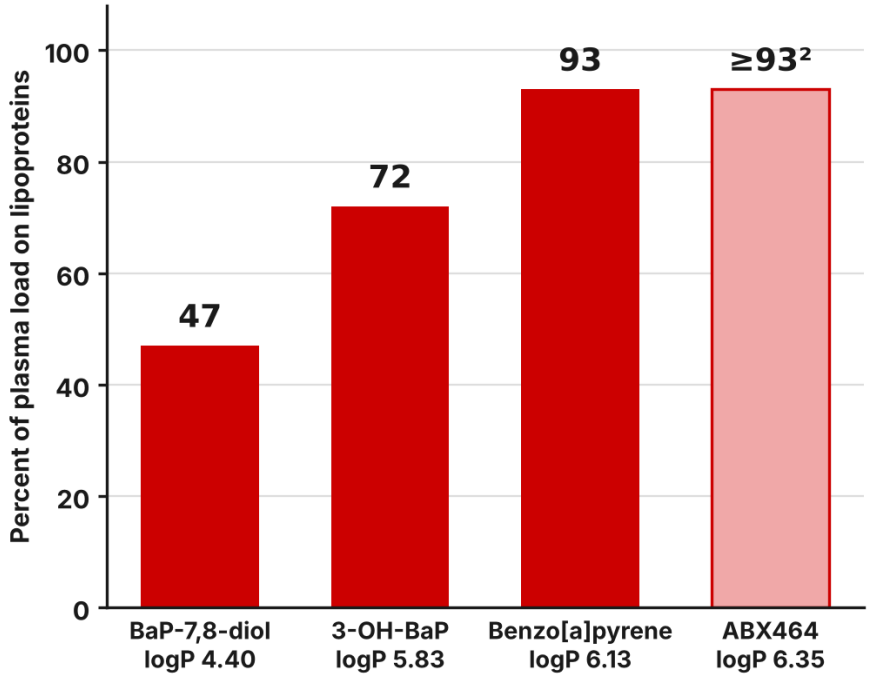
SR-B1 transcript runs 68% above matched normal prostate across 52 paired samples in TCGA PRAD (The Cancer Genome Atlas prostate adenocarcinoma cohort), p<0.0001. The tissues expressing high LDL receptor and SR-B1 include skin, colonic epithelium, pancreas, breast and prostate. That set contains the tissues carrying a Phase 3 malignancy and the colonic dysplasia. In breast and prostate these are also the tissues where AhR induced CYP1B1 converts estradiol to DNA-reactive metabolites.

These studies deliberately loaded drugs onto lipoprotein carriers. Sobot required a squalene tail to drive spontaneous loading. ABX464 may require no engineered carrier: its measured logP of 6.35 corresponds to an octanol/water partition coefficient of ~2.2 million:1, indicating an extreme preference for lipid over water. Our separate partition model estimates that up to ~98% of circulating parent drug may be lipoprotein-associated.

1. Vitols and Sobot are preclinical. Sobot's xenograft comparison used 3 animals per group and the human plasma distribution came from a 5-minute ex vivo incubation.
2. These studies delivered cytotoxic agents to established tumors on purpose. The claim here is about the route, not about equivalence of intent or of drug.
3. Sobot reports the 500-fold figure as affinity, derived from moles of drug per mole of particle.
4. Whether lipoprotein delivery preferentially reaches metastatic lesions is not sourced here.

Sources: Vitols et al. 1990; Versluis et al. 1998; Sobot et al. 2017; Abeshouse et al. 2015 (TCGA PRAD); Scorpion Capital analysis, modeling, estimates, and literature/publication review

Benzo[a]pyrene — a Group 1 carcinogen — is 93% lipoprotein-associated at logP 6.13; ABX464 is even more lipophilic at 6.35, supporting our inference that ABX464 could fall in the same or an even higher range of lipoprotein association.



Benzo[a]pyrene (BaP) is 93% associated with lipoproteins in plasma. Given the similar logP, we believe ABX464 will also be lipoprotein-associated.

Compound	logP[1]	Lipoprotein %, trace to saturation	Albumin-rich %, saturation
BaP-7,8-diol	4.40	35 to 47	53
3-OH-BaP	5.83	59 to 72	28
Benzo[a]pyrene	6.13	93	7
ABX464 parent	6.35	our inference, ≥93	?

Lipoprotein association increases as logP rises. It is driven by physical partitioning rather than specific binding, thus ABX464 would be expected to associate similarly. The solid tumors in Phase 3 came from tissues with high lipoprotein receptor expression. Precedent, physics and the 17 cancers are consistent with our hypothesis. We could find no protein binding or fractionation studies.

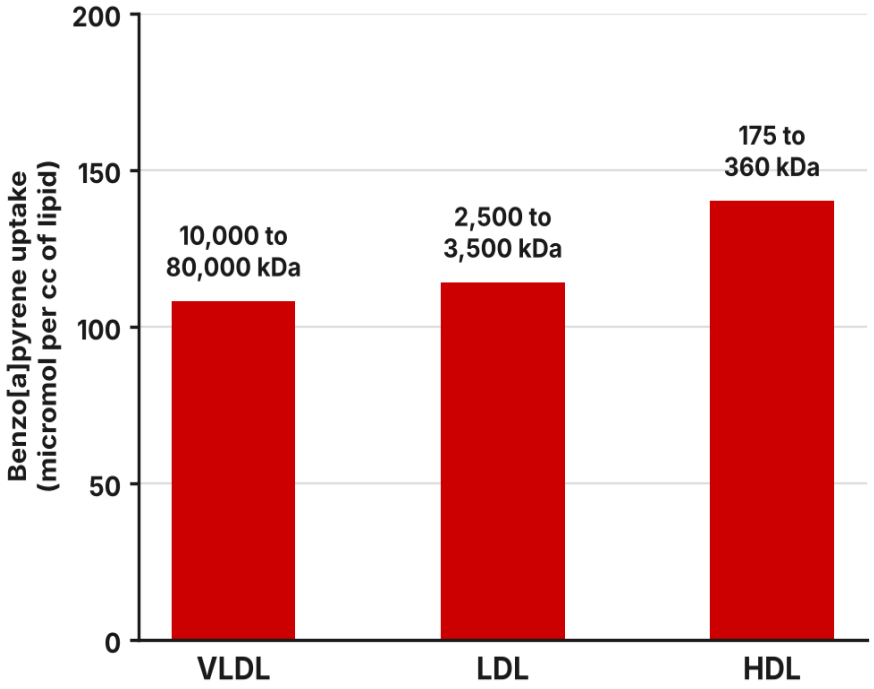
Lipoprotein association rises sharply across this series as logP increases. ABX464 has a measured logP of 6.35, slightly above benzo[a]pyrene at 6.13; we therefore infer that parent ABX464 may also be highly lipoprotein-associated. If so, lipoprotein uptake could provide a preferential delivery route into cells and tissues with high lipoprotein-receptor expression. The BaP comparison suggests a ≥93% association floor, while our separate partition model estimates ~98%. We could find no published ABX464 lipoprotein-fractionation data to test this prediction directly.

1. logP measured for benzo[a]pyrene and for ABX464 (HPLC, neutral pH 2 to 11). Metabolite logP calculated (RDKit Crippen) and anchored to the measured benzo[a]pyrene value.
2. Red bars are measured at saturation, from Shu and Nichols Tables IV and V, donor J.B. The pale bar is the ABX464 floor set by the benzo[a]pyrene value, not a measured value.

Sources: Shu and Nichols 1981; Hansch, Leo and Hoekman 1995; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Benzo[a]pyrene's 93% lipoprotein association is driven by simple lipid partitioning, not particle-specific binding -- supporting similarly high lipoprotein association for ABX464 given it is extremely lipophilic.

Nichols 1981 shows that BaP uptake scales with lipid content rather than particle size or protein identity — evidence for bulk-phase, mass-action partitioning. We therefore expect ABX464's extreme logP to favor the same physical process..



Lipid volume drives uptake. VLDL, LDL and HDL take up similar amounts of benzo[a]pyrene per unit of lipid despite very different particle sizes and proteins.

Partitioning, not specific binding. Benzo[a]pyrene remains ~93% lipoprotein-associated even at saturation.
Lipoproteins provide a large circulating lipid reservoir. Highly lipophilic neutral compounds naturally favor this environment over plasma water.

Implication for ABX464: Its logP of 6.35 should strongly favor lipoprotein association, creating a plausible route for increased delivery into tumors that overexpress LDLR or SR-B1. This remains an inference because ABX464 lipoprotein distribution has not been directly measured.

If ABX464 is highly lipoprotein-associated, tumor overexpression of LDLR and SR-B1 provides a plausible route for preferential delivery into receptor-rich tumors and premalignant lesions. This remains a hypothesis: we found no published ABX464 lipoprotein-fractionation data directly testing it. FDA recommends plasma protein binding and blood-to-plasma ratio before first-in-man.

1. Three particles of different size and different apolipoprotein composition take up a similar amount of benzo[a]pyrene per cubic centimeter of lipid, 108 to 140 micromol.
2. Shu and Nichols Table III, uptake per lipoprotein lipid volume; Table IV, trace and saturation distribution. ABX464 logP 6.35 measured by HPLC (CRO), neutral pH 2 to 11.

Sources: *Shu and Nichols 1981*; Scorpion Capital analysis, modeling, estimates, and literature/publication review

An early cancer signal does not require ABX464 to initiate tumors from scratch -- many adults especially older ones already harbor occult cancers, precancers, and premalignant cell clones that a tumor promoter could accelerate; Skin precancers affect ~40–60% of sun-exposed adults >40, while autopsy studies find incidental prostate cancer in a majority of older men. Chronic AhR activation provides a plausible mechanism for promoting or progressing these pre-existing lesions into active malignancies.

Abivax attributes some of the cancers to pre-existing disease. However:

- **Pre-existing disease does not exclude drug promotion.** Many adults harbor indolent cancers, precancers and premalignant cell clones that may never become clinically apparent.
- **Promotion can require fewer additional biological steps than de novo tumor initiation.** A chronic tumor-promoting signal could accelerate a lesion already close to malignant progression, allowing cancers to appear relatively early after treatment begins.
- **This is the hypothesis tested in the following slides:** whether sustained AhR signaling can remove restraints on survival, invasion, angiogenesis and tumor expansion in cells that are already partially transformed.

High prevalence of occult lesions found in people with no clinical cancer - autopsy finds histologically malignant lesions in people who died of other causes. Sequencing finds cancer-driver mutations in tissue that looks normal. Prevalence increases with age and is already substantial before 40.

Tissue	Occult lesion	Prevalence
Prostate	Invasive carcinoma (autopsy)	40 to 70% of older men
Thyroid	Papillary carcinoma (autopsy)	4 to 36%
Breast	Carcinoma or DCIS (autopsy)	7 to 39% across series
Skin	Actinic keratosis (precancer)	14% overall; 40 to 60% over age 40 in sun-exposed regions
Pancreas	PanIN (precancer)	Low-grade in 77 to 86% of aging pancreata; high-grade (PanIN-3) in 4%

Tissue	What was measured	Prevalence - older donors	Source
Esophagus	NOTCH1-mutant epithelium, % of tissue	30 to 80% in middle-aged and elderly	Martincorena et al. 2018
Skin	Driver-mutant cells, % of cells	18 to 32%, donors aged 55 to 73	Martincorena et al. 2015
Blood and marrow	Clonal hematopoiesis, % of people	5.6% at 60 to 69; about 10% over 70	Jaiswal et al. 2014

Sources: Bell et al. 2015; Welch and Black 1997; Harach et al. 1985; Flohil et al. 2013; Matsuda et al. 2017; Folkman and Kalluri 2004; Martincorena et al. 2018; Martincorena et al. 2015; Jaiswal et al. 2014; ; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Autopsy studies and population cohorts show that occult cancers and precancerous lesions are common in older adults -- including breast, prostate and skin lesions similar to malignancies observed in ABX464 studies. A sample of the literature is shown below. Studies focused on blood/marrow, meningioma, and other cancers report similar findings, but are not shown.

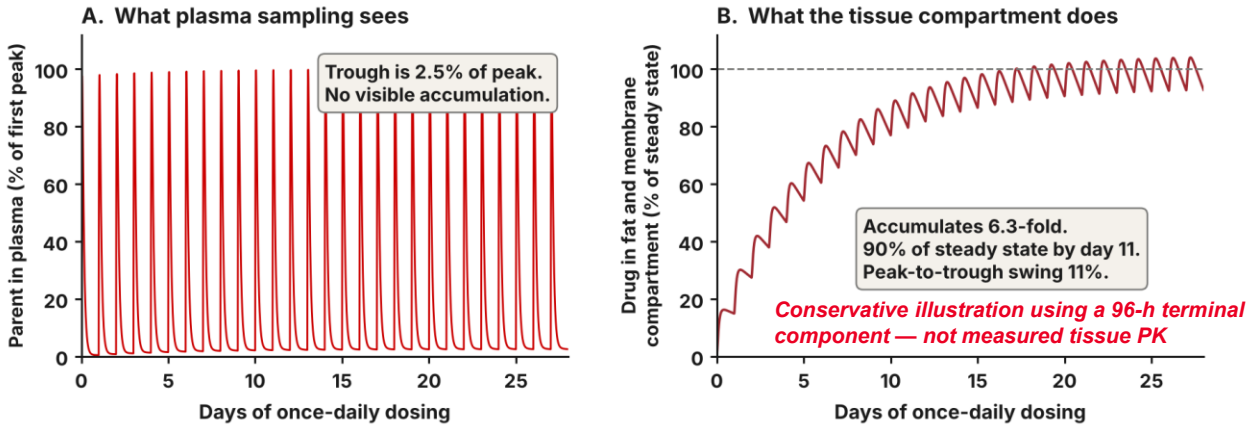
Literature review – precancer prevalence in breast, skin, prostate

Prevalence of incidental breast cancer and precursor lesions in autopsy studies: a systematic review and meta-analysis	***A systematic review/meta-analysis of 2,363 autopsies found 19.5% of women had an incidental breast cancer or precursor lesion: ~0.85% invasive cancer, 8.9% in-situ cancer and 9.8% atypical hyperplasia.***
Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study	***In the Rotterdam Study, mean age 72, actinic keratoses were present in 49% of men and 28% of women.***
Non-melanoma skin cancer and solar keratoses. I. Methods and descriptive results of the South Wales Skin Cancer Study	***Another population study of adults ≥60 found solar keratoses in 23% and skin cancer in 2%.***
Prevalence of incidental prostate cancer: A systematic review of autopsy studies	***A systematic review of 29 autopsy studies estimated incidental prostate cancer prevalence rising from ~5% in men under 30 to ~59% in men over 79.***

Sources: https://pubmed.ncbi.nlm.nih.gov/29197354/; https://pubmed.ncbi.nlm.nih.gov/23510990/; https://pubmed.ncbi.nlm.nih.gov/25821151/;

ABX464's PK could turn AhR activation from a transient physiological pulse into a chronic signal – duration of AhR signaling raises carcinogenic concerns. Our reanalysis identifies multi-day to ~10–20+ day terminal components consistent with slow tissue release, so once-daily dosing can repeatedly reload tissues before prior drug-related material has cleared.

Slow tissue release can sustain drug exposure that is largely missed by plasma sampling — the 96-hour tissue component modeled below[1] is conservative relative to the slower terminal components identified in our PK reanalysis.[2]



Illustrative plasma-versus-tissue PK. **Panel A shows why plasma sampling can make ABX464 appear short-lived: parent concentrations spike and fall rapidly between doses. Panel B is a conservative simulation using a 96-hour terminal tissue component to illustrate the consequence of slow tissue release under once-daily dosing — repeated doses accumulate and tissue concentrations fluctuate far less than plasma.**

Our PK analysis now suggests even slower terminal behavior: the published ~4-day N-Glu phase may itself reflect slow release of parent from tissue, while our reanalysis identifies additional ~10-day and ~20+ day terminal components. Thus, the 96-hour simulation shown here should be viewed as a conservative illustration, not our estimate of ABX464's true terminal tissue half-life.

1. Two-compartment simulation with first-order absorption, distribution half-life 1.5 h, terminal half-life 96 h and once-daily dosing. Illustrative model; not measured tissue PK.
2. Our reanalysis of published plasma concentration-time data identifies additional ~10-day and ~20+ day terminal components in N-Glu, consistent with prolonged release of drug-related material from tissue compartments. These are model-derived/inferred terminal components, not directly measured tissue half-lives.

Sources: Scherrer et al. 2017; Rannug 2020; Scorpion Capital analysis, modeling, estimates, and literature/publication review

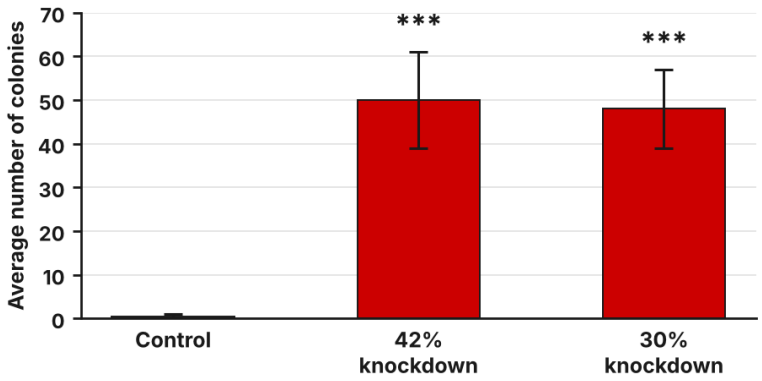
Partial AHRR loss alone gives non-tumorigenic human breast epithelial cells a hallmark of malignant transformation -- anchorage-independent growth appears without adding an oncogene. The Phase 3 breast cancer arose from the same cell lineage in which weakening the AhR feedback brake has been shown sufficient to produce this transformation phenotype.

MCF10A is a non-transformed, non-tumorigenic human mammary epithelial cell line with no activating oncogene. Zudaire et al. reduced AHRR expression by only ~30–42%; both knockdowns enabled robust anchorage-independent colony formation, while control cells formed essentially none.The breast cancer reported in Phase 3 was a Grade 2 invasive ductal carcinoma, an epithelial tumor from the same cell type.

AHRR intact (MCF10A-E). Non-tumorigenic MCF10A cells form essentially no colonies in soft agar. Without anchorage, a normal cell does not grow.

AHRR silenced (MCF10A-F/G). MCF10A cells form colonies in soft agar without anchorage. AHRR loss produces anchorage-independent growth.

Zudaire et al., JCI 2008 — partial AHRR knockdown converts non-tumorigenic MCF10A breast epithelial cells from essentially zero to ~50 soft-agar colonies



- **Model: MCF10A, a non-transformed, non-tumorigenic human mammary epithelial line without an activating oncogene**
- **AHRR was silenced by siRNA (two independent constructs), with an empty-vector control**
- **Knockdown was confirmed by real-time RT-PCR (30 to 42% reduction in AHRR mRNA; Suppl. Fig. 3B)**
- **Transfectants were seeded in soft agar. Cultures were maintained at 37°C for 4 weeks, after which colonies larger than 0.1 mm were quantified**
- **Colony formation was scored relative to the empty-vector control; assays were performed in triplicate**

Anchorage-independent growth is a hallmark of transformation. Growth in soft agar correlates with tumor-forming potential. Silencing the AHRR repressor with no additional oncogene is sufficient to give a normal breast cell the ability to proliferate in soft agar.

Partial AHRR loss is sufficient to produce a transformation phenotype. AHRR knockdown of only ~30–42% enabled previously non-clonogenic MCF10A cells to grow in soft agar.. Human premalignant lesions already show partial AHRR loss — including colon polyps in Zudaire et al. — providing a plausible setting in which AhR feedback is already weakened before overt malignancy.

1. MCF10A soft-agar colony counts. Control (AHRR intact) formed essentially no colonies; AHRR knockdown of 42% and 30% produced about 50 and 48 colonies, both P<0.001 (***). Zudaire 2008, Fig. 2F (colony counts) and Suppl. Fig. 3B (knockdown).
2. This figure shows anchorage-independent growth, a transformation hallmark. MCF10A tumor formation in animals was not tested here.

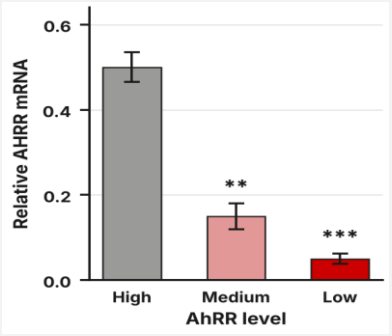
Sources: Zudaire et al. 2008; Soule et al. 1990; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Lowering AHRR alone makes human lung cancer cells markedly more malignant -- apoptosis falls while angiogenesis, migration and invasion rise several-fold

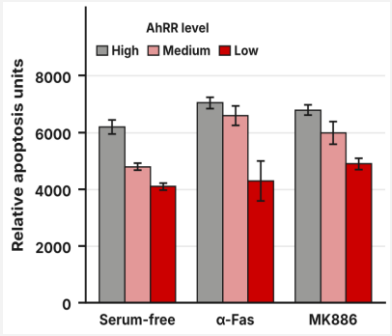
AHRR is silenced in multiple human cancers, weakening the AhR feedback brake. Zudaire tested whether reducing AHRR alone was sufficient to promote aggressive cancer phenotypes in a human lung cancer cell line.

Zudaire et al., JCI 2008 — AHRR knockdown shifts A549 lung cancer cells toward a more aggressive phenotype: less apoptosis, more angiogenesis, migration and invasion

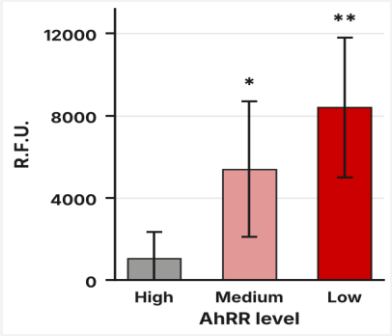
AhRR expression
Zudaire 2008, Suppl. Fig. 3a



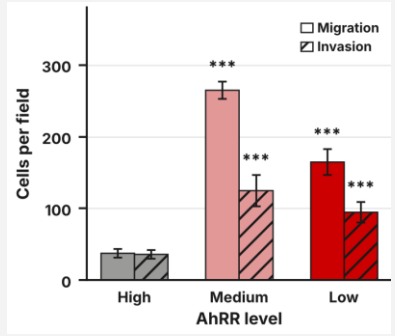
Apoptosis
Zudaire 2008, Fig. 3A



Angiogenesis
Zudaire 2008, Fig. 3B



Migration and invasion
Zudaire 2008, Fig. 3C



Study design: Three A549 lung adenocarcinoma lines differ only in how much AhRR they carry. The high line received an empty vector. Two further lines were engineered with silencing RNA and selected at 70% knockdown (medium, pink) and 90% knockdown (low, red).[1] Apoptosis, migration, and invasion were assessed in vitro, and angiogenesis in vivo.

Methods: Apoptosis was measured as caspase-3/7 activity in 96-well plates, after an overnight challenge with serum-free medium, anti-Fas at 5 µg/ml, or MK886 at 0.5 µM. Migration was measured as chemotaxis across an 8 µm pore membrane in 96-well ChemoTx plates after 4 hours. Invasion used the same transwell format with a Matrigel-coated membrane. Angiogenesis was measured by the directed in vivo angiogenesis assay (DIVAA), where 10,000 cells in a gel were implanted into athymic nude mice and vessel ingrowth was quantified after 11 days.

Results. In the AhRR knockdown lines, angiogenesis increased 5-fold and 8-fold over control and apoptosis decreased, while migration increased 7-fold in the medium line and 4.5-fold in the low line.[2] Every measure of tumorigenicity increased as AhRR fell.

Our conclusions: New vessels nourish the growing tumor. Less apoptosis lets a damaged clone persist and expand. Migration and invasion carry the cells past their borders. All three followed from removing the brake on AhR, with no added agonist. The earlier slide showed the same effect in a non-transformed human breast epithelial line, and this one shows that further weakening AHRR in an established lung cancer line promotes multiple aggressive phenotypes.

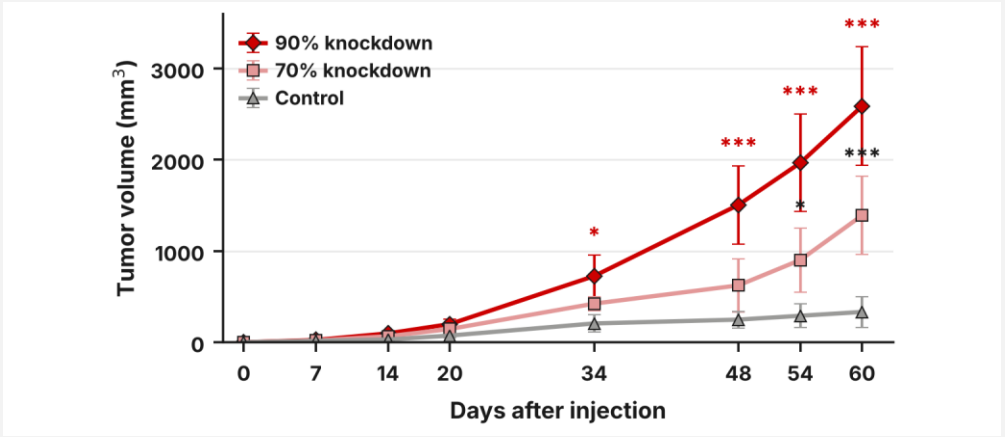
1. High AhRR = A549E (empty-vector control), medium = A549F, low = A549G, both AHRR siRNA transfectants selected in 800 µg/ml geneticin. AHRR mRNA from Supplementary Figure 3a.
2. Angiogenesis and apoptosis scale with AhRR loss. Migration does not: the medium-AhRR line exceeds the low-AhRR line, 7-fold against 4.5-fold over control.

Sources: Zudaire et al. 2008; Scorpion Capital analysis, modeling, estimates, and literature/publication review

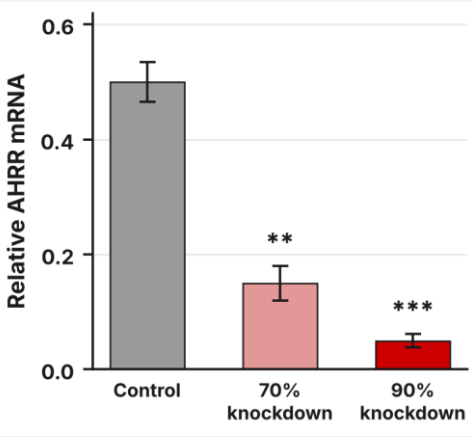
AHRR loss does not simply make cancer cells divide faster -- it leads to sustained tumor expansion. In mice, AHRR-knockdown tumors keep expanding, reaching ~3× and ~7× the control tumor size by 8 weeks.

Zudaire et al., JCI 2008 — AHRR knockdown drives sustained A549 xenograft expansion: ~3× and ~7× larger tumors at eight weeks

A549 Tumor growth in nude mice



Relative AhRR expression in 3 A549 clones



Methods. **Three A549 cell lines, the empty-vector control and the two AhRR knockdown lines at 70% and 90% from the previous slide,[1] were tested for tumorigenicity in vivo. Cells were implanted as xenografts into athymic nude mice (n = 10 per group) and tumor volume was measured for 60 days.**

Results. **The xenografts initially tracked relatively closely, then separated markedly after ~3–4 weeks. By eight weeks, the ~70% and ~90% AHRR-knockdown tumors were ~3-fold and ~7-fold larger than control, respectively. Both knockdown tumors continued growing through day 60, while the control plateaued at ~330 mm³ from roughly day 34 onward.**

The key result is sustained tumor expansion after AHRR loss. Control xenografts plateaued while both AHRR-knockdown lines continued to grow, with the strongest effect in the deepest knockdown. Together with Zudaire's apoptosis, angiogenesis, migration and invasion experiments, this supports AHRR as a tumor-suppressive brake whose loss promotes multiple features of tumor progression.

1. Control = A549E (empty-vector transfectant), 70% knockdown = A549F, 90% knockdown = A549G, both AHRR siRNA transfectants selected in 800 µg/ml geneticin. AHRR mRNA from Zudaire 2008 Supplementary Figure 3a.
2. Doubling times over day 14 to 34 were 7.2 days (control), 7.5 days (70% knockdown), and 6.9 days (90% knockdown). Over day 14 to 60 they were 14.6, 11.5, and 9.9 days. Rate metrics were derived by Scorpion Capital from Figure 2l; the paper reports fold volume only, 3-fold and 7-fold at eight weeks.
3. Athymic nude mice lack mature T cells and retain macrophages, neutrophils, dendritic cells, complement, and B cells, with natural killer activity above wild-type.

Sources: Zudaire et al. 2008; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Human precancers progressively silence AHRR as they advance, weakening the feedback brake that normally shuts down AhR signaling – a vulnerable setting where sustained AhR activation by a chronic agonist could preferentially accelerate lesions already closest to malignant progression.

Zudaire et al., JCI 2008 — AHRR promoter methylation is absent in matched normal tissues but emerges in precancers and increases with malignant progression across multiple human cancers

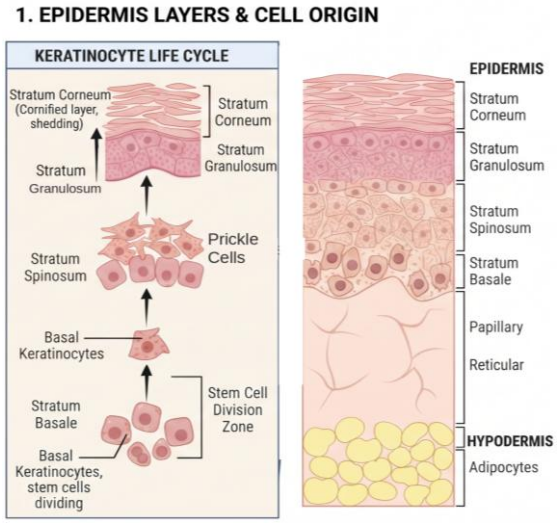
Tumor type	No. studied	Methylated (%) Any methylation	UM/M (%) Partly methylated	M/M (%) Fully methylated
Normal testis	**4**	**0**	**0**	**0**
Testicular cancer	79	44.3%	42.8	57.2
Seminoma	15	13.3%	50	50
Nonseminoma (higher grade)	64	51.6%	42.4	57.6
Normal cervix	**44**	**0**	**0**	**0**
Cervical cancer	66	95.5%	81	19
Cell lines	9	100%	11.1	88.9
Primary tumors	57	94.7%	92.6	7.4
Precancer, low-grade	48	4.2%	ND	ND
Precancer, high-grade	39	41%	ND	ND
Normal ovary	**2**	**0**	**0**	**0**
Ovarian cancer	14	100%	21.4	78.6
Normal esophagus	**8**	**0**	**ND**	**ND**
Low-grade dysplasia	8	0	ND	ND
High-grade dysplasia	7	28%	ND	ND
Esophageal tumor	23	52%	ND	ND
Tumor only (no normal tissue available but all normal tissues above were zero, no methylation, n = 58 samples)				
Prostate cancer	6	67%	ND	ND
Colon cancer	8	100%	ND	ND

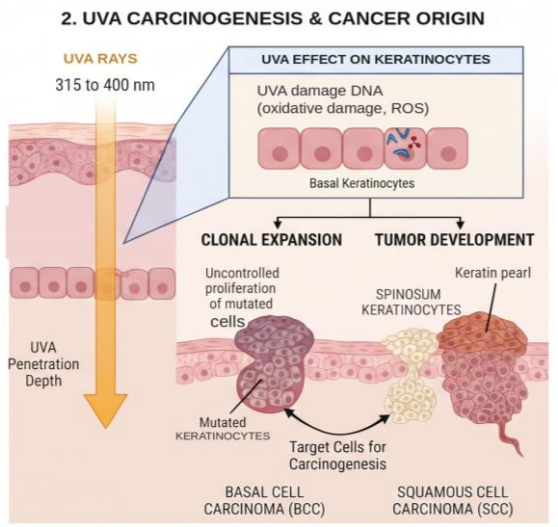
Methylated (%) is the share of samples with any AHRR methylation. Of those, UM/M = an unmethylated and a methylated allele both present (one copy still active, partial silencing); M/M = only the methylated allele present (both copies silenced, complete loss). ND, not done. Normals are shaded and each cancer is indented beneath its matched normal; prostate and colon had no matched normal tissue analyzed.

Sources: Zudaire et al. 2008; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Chapter 18. Scorpion Capital's independent lab experiments indicate obefazimod's concerning potential for UVA-driven skin cancer

UVA reaches the dividing basal keratinocytes that give rise to BCC and SCC — the exact compartment where a UVA-absorbing drug could create persistent DNA damage and mutations that lead to skin cancer





Panel 1 — epidermal layers and cellular origins of skin cancer

The epidermis renews from dividing basal keratinocytes. Their daughter cells migrate upward, stop dividing and are eventually shed, while the basal cells remain and continually replenish the epidermis. Persistent mutations in this dividing compartment can therefore be propagated into daughter cells and give rise to BCC and SCC.

Panel 2 — UVA penetration and DNA damage

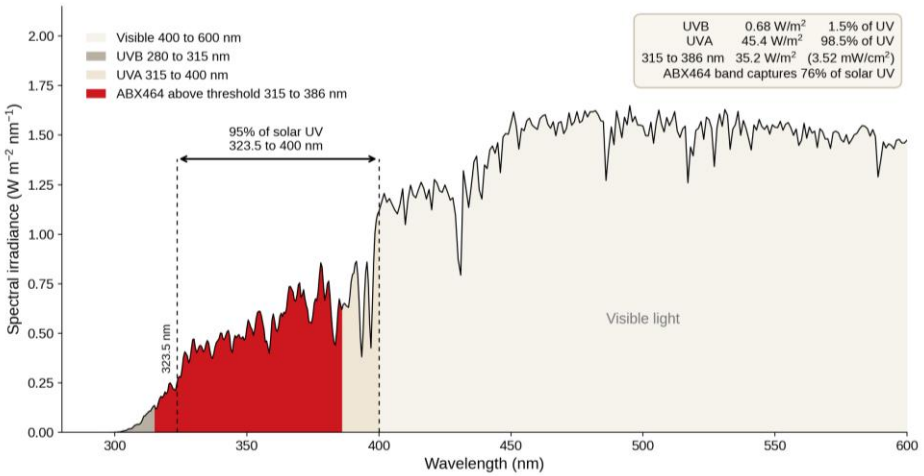
UVA reaches the dividing basal layer. UVA penetrates more deeply than UVB, reaching through the epidermis into the basal layer and dermis. A drug present at this depth that absorbs UVA can be repeatedly photoexcited and generate reactive oxygen species and oxidative damage. Because basal keratinocytes continue dividing rather than being shed, damage in this compartment has the potential to persist and clonally expand.

Sources: Halprin 1972; Meinhardt et al. 2008; Mouret et al. 2006; ICH S10 2015; ASTM G173-03; Scorpion Capital, ABX464 DLS and Autofluorescence experiment, 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our laboratory characterization shows that ABX464's photoreactive band overlaps wavelengths carrying ~76% of all solar UV reaching the ground — spanning much of the deeply penetrating UVA spectrum. Its broad overlap with solar UVA increases the range of wavelengths capable of photoexciting the molecule.

Ground-level solar radiation includes a UVA band that can penetrate to dividing basal keratinocytes with sufficient photon energy to support ROS-generating photochemistry. ABX464 absorbs broadly within this region (red).

ASTM G173-03 solar spectrum + our UV/Vis data — ABX464's photoreactive band overlaps ~76% of ground-level solar UV



ASTM G173-03 reference solar spectrum, AM1.5 global, retrieved via pvlib. Bands and cumulative fractions integrated by trapezoid rule. Percentages are of ultraviolet only (280 to 400 nm). The ABX464 span is where its measured molar extinction coefficient exceeds the ICH S10 threshold of 1,000 $M^{-1}cm^{-1}$. AM1.5 is a 48.2 degree solar zenith angle; at higher sun the 95% boundary shifts down a few nm.

A photoactive drug can only be excited by wavelengths it absorbs. Our UV/Vis experiment shows that ABX464 absorbs above the ICH S10 photoreactivity threshold across 315–386 nm, overlapping much of the solar UVA spectrum. This creates repeated opportunities for photoexcitation in sun-exposed tissue.[1]

UVA accounts for ~98.5% of ground-level solar UV. ABX464's above-threshold absorption band from 315–386 nm contains ~76% of total solar UV irradiance. Above ~400 nm, ABX464 absorption falls to near baseline.

UVA combines high ground-level abundance with deeper skin penetration than UVB, reaching the basal epidermis and dermis. Photons across ABX464's absorption band also carry sufficient energy to drive photochemical reactions if an appropriate excited-state pathway is available.[3]

[1] Excitation rate $R = \int \sigma(\lambda)\cdot q(\lambda)\, d\lambda$, with $\sigma(\lambda) = 3.82\times10^{-21}\cdot\varepsilon(\lambda)$ (ε in $M^{-1}cm^{-1}$). The rate rises with the overlap between the absorption and the solar photon flux.

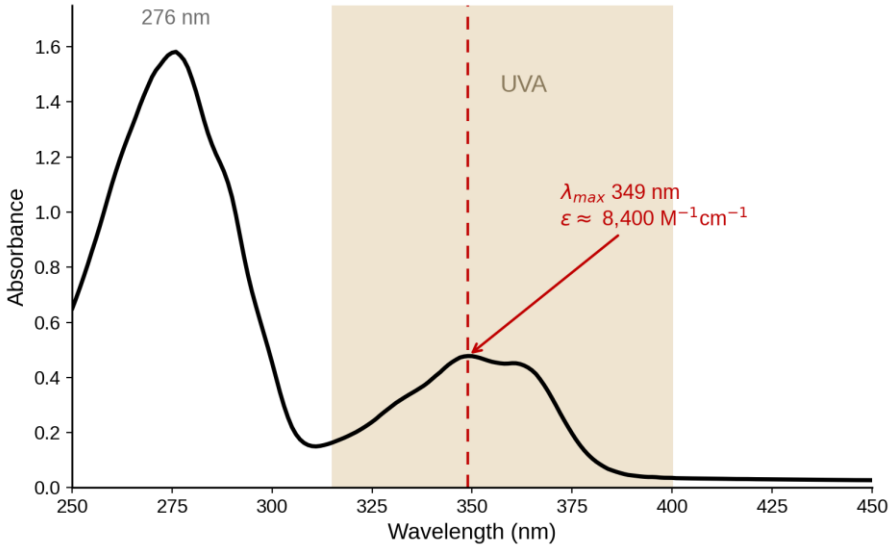
[2] Ground-level solar UV: UVA 45.4 W/m² (98.5%), UVB 0.68 W/m² (1.5%). The ABX464 band, 315 to 386 nm where ε exceeds 1,000 $M^{-1}cm^{-1}$, carries 35.2 W/m², 76% of total UV. ASTM G173-03 AM1.5 global, trapezoid rule, 48.2° zenith.

[3] Photon energy $E = hc/\lambda \approx 1240/\lambda$ (eV, λ in nm): 3.94 eV at 315 nm, 3.10 eV at 400 nm. Penetration depth increases with wavelength.

Sources: Meinhardt et al. 2008; Mouret et al. 2006; ICH S10 2015; ASTM G173-03; Scorpion Capital, ABX464 DLS and Autofluorescence experiment 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Our UV/Vis experiment puts ABX464 8.4× above the ICH S10 photosafety screening threshold at 349 nm — with strong absorption extending across a broad UVA band. ABX464's extreme lipophilicity predicts strong partitioning into cellular membranes once the drug reaches skin, potentially placing a photoexcited molecule near oxidizable membrane lipids.

Scorpion Capital UV/Vis experiment — ABX464 shows a broad UVA absorption band with λmax 349 nm (ε ≈ 8,400 $M^{-1}cm^{-1}$), 8.4× the ICH S10 photosafety screening threshold



Methods, absorbance spectrum: We recorded the absorbance spectrum of ABX464 on a PerkinElmer LAMBDA 365 UV/Vis spectrophotometer. ABX464 was dissolved in acetonitrile (HPLC grade, Sigma-Aldrich) at 57 µM and scanned from 200 to 700 nm in a 1 cm quartz cuvette at 25 °C against a matched acetonitrile blank, using the instrument's default settings (1 nm data interval). The molar extinction coefficient was calculated from the peak absorbances using the Beer-Lambert relation, ε = A/(cl).[1]

Why ABX464's logP matters: ABX464 is an extremely lipophilic neutral molecule (measured logP 6.35), so once present in skin it would be expected to partition strongly into keratinocyte membranes. That could increase the local membrane concentration of a UVA-absorbing chromophore near oxidizable lipids. We found no published parent-drug skin-distribution study directly testing this prediction.

Results: ABX464 showed two absorption maxima in the long-wavelength UVA region, at 349 nm (ε 8,400 $M^{-1}cm^{-1}$) and 360 nm (ε 7,900 $M^{-1}cm^{-1}$), the first more than eightfold above the ICH S10 screening threshold of 1,000 $M^{-1}cm^{-1}$. The two maxima were about 876 cm^{-1} apart, consistent with vibronic progression (Lakowicz 2006; Turro et al. 2010). Such a vibronic pattern is consistent with a relatively rigid, planar chromophore whose geometry changes little upon excitation, consistent with ABX464's planar aromatic structure (Turro et al. 2010). The two maxima were separated by a shallow trough, with the second peak nearly as intense as the first, so the molecule absorbs strongly across its a wide band, with significant absorption observed out to 380 nm.

[1] ε is the molar extinction coefficient, obtained from the Beer-Lambert relation ε = A/(cl), where A is the measured absorbance (dimensionless), c is the molar concentration of ABX464 in solution (M), and l is the optical path length of the cuvette (cm). ε is reported in $M^{-1}cm^{-1}$.

Sources: Lakowicz 2006; Turro et al. 2010; Scorpion Capital, ABX464 absorption spectrum experiment, 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's Phase 2b protocol states that ABX464-N-Glu was phototoxic in a nonclinical model at clinically relevant exposures and required sun protection -- but the paragraph is silent about the parent compound, which we characterized in the laboratory. The publicly available ABTECT-1/2 Phase 3 protocols heavily redact the relevant AESI sections, with no visible mention of phototoxicity. Although ABVX later confirmed skin-lesion surveillance in Phase 3, neither the 2022 protocol nor Jun 2026 presentation identify the underlying phototoxicity study, methods, or report.

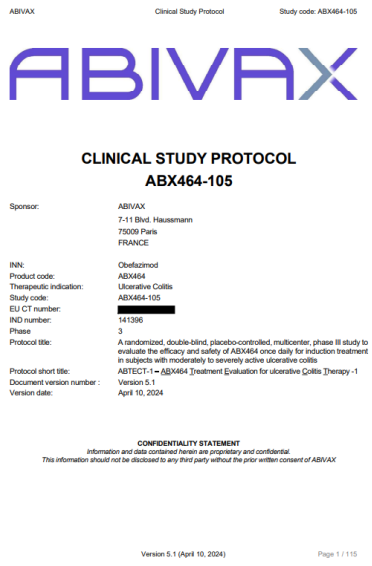
Phase 2b protocol, ABX464-104 v5.1 (11 July 2022), p39, §8.2 AESI "Skin Lesions" - excerpt

Skin Lesions (regardless of its severity)

The AESI "skin lesion" should be broadly captured by the site physician. Subjects are informed via the ICF that oral administration of ABX464-N-Glu was phototoxic in a nonclinical model at clinically relevant exposure levels. To mitigate this risk, subjects must comply with usual public recommendations for sun protection, such as: use shade wisely, wear protective clothing (hat, sunglasses), use sunscreen (with a sun protective factor [SPF] of 15 or higher), and limit time spent in mid-day sun or strong sunlight. Subjects experiencing skin lesion(s) will be instructed to contact the site study coordinator or investigator and to take a picture of the skin lesion for medical assessment. The site investigator will complete a specific skin lesion AESI reporting form (Appendix # 4). Additionally, the skin lesion AESI form may be supplemented by pictures of the affected skin region(s) taken by the subject, at their discretion. The pseudonymized skin lesion AESI form will be reviewed by a central dermatologist, to investigate a potential for photosensitivity. A pseudonymized medical report will be provided by the central dermatologist.

"Subjects are informed via the ICF that oral administration of ABX464-N-Glu was phototoxic in a nonclinical model at clinically relevant exposure levels. To mitigate this risk, subjects must comply with usual public recommendations for sun protection, such as: use shade wisely, wear protective clothing (hat, sunglasses), use sunscreen (with a sun protective factor [SPF] of 15 or higher), and limit time spent in mid-day sun or strong sunlight."

Phase 3 protocols: AESI sections heavily redacted, preventing independent verification of phototoxicity language — ABTECT-1 and ABTECT-2 shown below, respectively


ABIVAX Clinical Study Protocol Study code: ABX464-105

ABIVAX

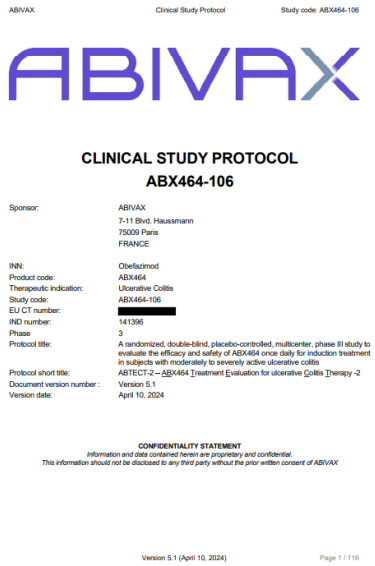
CLINICAL STUDY PROTOCOL
ABX464-105

Sponsor: ABIVAX, 7-11 Blvd. Haussmann, 75009 Paris, FRANCE

INN: Obefazimod
Product code: ABX464
Therapeutic indication: Ulcerative Colitis
Study code: ABX464-105
EU CT number: [redacted]
IND number: 141396
Phase 3
Protocol title: A randomized, double-blind, placebo-controlled, multicenter, phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis
Protocol short title: ABTECT-1 – ABX464 Treatment Evaluation for ulcerative Colitis Therapy -1
Document version number: Version 5.1
Version date: April 10, 2024

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ABIVAX Clinical Study Protocol Study code: ABX464-106

ABIVAX

CLINICAL STUDY PROTOCOL
ABX464-106

Sponsor: ABIVAX, 7-11 Blvd. Haussmann, 75009 Paris, FRANCE

INN: Obefazimod
Product code: ABX464
Therapeutic indication: Ulcerative Colitis
Study code: ABX464-106
EU CT number: [redacted]
IND number: 141396
Phase 3
Protocol title: A randomized, double-blind, placebo-controlled, multicenter, phase III study to evaluate the efficacy and safety of ABX464 once daily for induction treatment in subjects with moderately to severely active ulcerative colitis
Protocol short title: ABTECT-2 – ABX464 Treatment Evaluation for ulcerative Colitis Therapy -2
Document version number: Version 5.1
Version date: April 10, 2024

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Version 5.1 (April 10, 2024) Page 1 / 116

Sources: Phase 2b clinical study protocol, https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf; ABTECT-1 protocol, v5.1 dated Apr 10, 2024, https://cdn.clinicaltrials.gov/large-docs/03/NCT05507203/Prot_000.pdf; ABTECT-2 protocol, v5.1 dated Apr 10, 2024, https://cdn.clinicaltrials.gov/large-docs/16/NCT05507216/Prot_000.pdf; ABVX investor presentation, June 2026; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Across Phase 3 maintenance, 10 non-melanoma skin cancers were reported: 6 at 50 mg, 3 at 25 mg and only 1 on placebo – a dose-ordered pattern concentrated on active drug. Four active-drug cases were assessed as possibly or probably related to study drug; one additional SCC was reported in Phase 2. The high-dose signal remains ~4× higher after exposure normalization in placebo-controlled Part 1.

The Phase 3 NMSC counts are dose-ordered -- 6 at 50 mg, 3 at 25 mg and 1 on placebo -- raising a treatment-related safety signal. Importantly, ABVX's disclosures report that investigators assessed two Part 1 NMSCs as "possibly related" and two Part 2 NMSCs as "probably related" to study drug. The high-dose signal persists after exposure normalization in placebo-controlled Part 1: our reconstructed 50 mg NMSC rate is ~2.7 per 100 patient-years vs 0.68 on placebo -- ~4× higher[1].

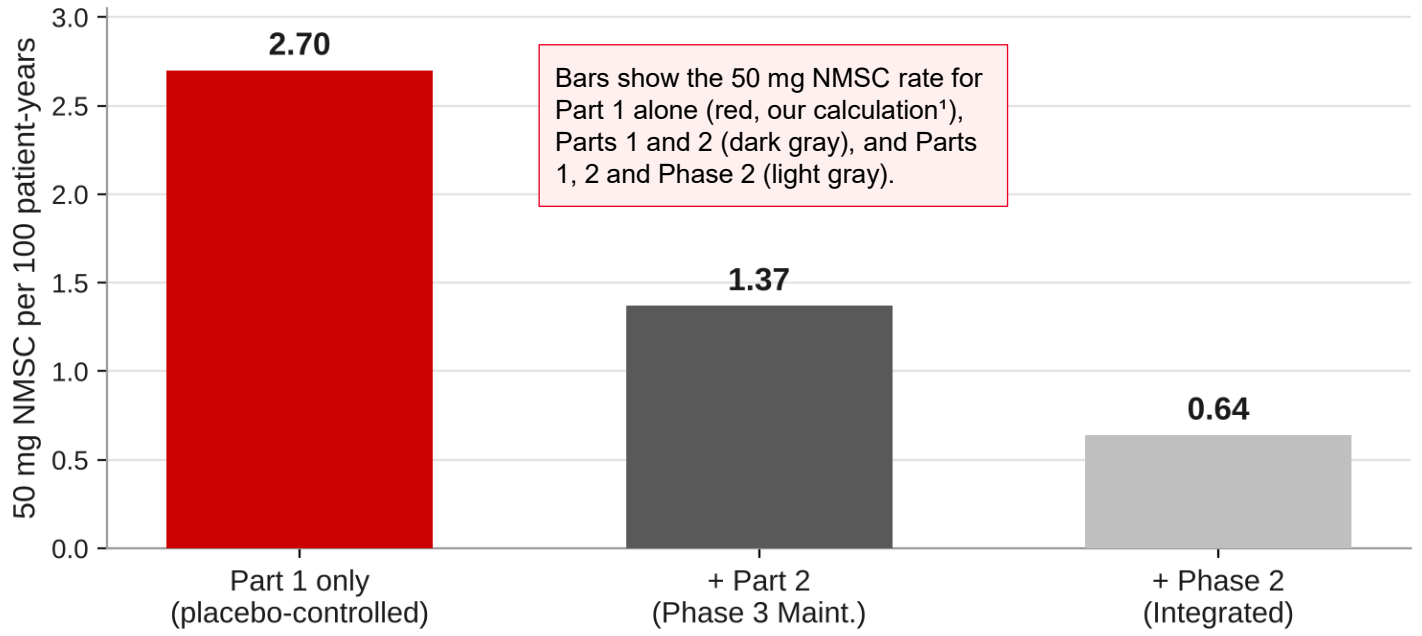
Reported malignancies across Abivax's Phase 2/3 UC program -- dose, exposure and investigator causality assessments

Cancer	Study	Dose	Age	Exposure	Investigator assessment
Malignancies excluding non-melanoma skin cancer					
Malignant meningioma, grade III	Ph2 (104)	50 mg	65+	14.0 mo	Not related
Prostate, stage I, GG2	Ph3 induction (105)	50 mg	60+	0.5 mo	Not related
Breast, grade 2 ductal	Ph3 maint. Part 1	50 mg	65+	6.8 mo	Unlikely related
Prostate, Gleason 7	Ph3 maint. Part 1	50 mg	50+	8.5 mo	Unlikely related
Myeloproliferative neoplasm	Ph3 maint. Part 2	50 mg	40+	7.4 mo	Not related
Prostate, Gleason 7B, cT2N0M0	Ph3 maint. Part 2	50 mg	55+	3.4 mo	Not related
Non-melanoma skin cancers					
BCC	Ph3 maint. Part 1	Placebo	70+	1.9 mo	Not related
SCC	Ph3 maint. Part 1	25 mg	60+	8.7 mo	Not related
BCC	Ph3 maint. Part 1	50 mg	70+	6.1 mo	Unlikely related
BCC	Ph3 maint. Part 1	50 mg	45+	5.5 mo	Not related
SCC	Ph3 maint. Part 1	50 mg	70+	3.5 mo	Possibly related
SCC	Ph3 maint. Part 1	50 mg	60+	2.8 mo	Possibly related
BCC	Ph3 maint. Part 2	25 mg	50+	8.1 mo	Unlikely related
SCC	Ph3 maint. Part 2	25 mg	75+	8.3 mo	Probably related
BCC	Ph3 maint. Part 2	50 mg	40+	10.4 mo	Probably related
SCC	Ph3 maint. Part 2	50 mg	55+	4.6 mo	Not related
SCC	Ph2 (103/104/108)	100, 50, 25 mg	55+	28.9 mo	Unlikely related

Sources/notes: Abivax, ABTECT maintenance Part 1 results (1 June 2026); Abivax, ABTECT maintenance Part 2 topline (2026); Abivax, integrated summary of safety, ABTECT induction (DDW 2026); Vermeire et al. 2022; Scorpion Capital analysis, modeling, estimates, and literature/publication review; [1] Part 1 50 mg rate reconstructed from Abivax-disclosed NMSC event counts and exposure-adjusted incidence rates for Part 1+2 and Part 2 alone; because disclosed rates are rounded, the resulting Part 1 estimate is approximate (~2.7 per 100 patient-years). The placebo rate of 0.68 per 100 patient-years is directly reported; Part 2 had no placebo arm.

ABVX reports NMSC rates for pooled datasets, but not Part 1 alone. Reconstructing placebo-controlled Part 1 yields the highest 50 mg rate at ~2.70 per 100 patient-years; the reported rate falls to 1.37 after Part 2 is added and to 0.64 in the integrated Phase 2+3 dataset. The high-dose signal is therefore most pronounced in the randomized, placebo-controlled cohort and progressively dilutes as lower-rate exposure cohorts are added.

50 mg NMSC incidence across progressively broader Abivax analysis sets — reconstructed Part 1 vs. reported pooled rate



[1] Abivax reports 50 mg NMSC EAIRs for Phase 3 Maintenance Parts 1+2 combined (1.37; 6 events), Part 2 alone (0.69; 2 events), and the integrated Phase 2+3 program (0.64), but we found no Part 1-only EAIR. We reconstruct Part 1 from the reported event counts and exposure-adjusted rates: 6/1.37 × 100 ≈ 438 patient-years for Parts 1+2; 2/0.69 × 100 ≈ 290 patient-years for Part 2; therefore Part 1 contributes ≈148 patient-years and 4 events, implying ≈2.70 NMSC events per 100 patient-years. Because Abivax reports EAIRs rounded to two decimals, the reconstructed Part 1 rate is approximate.

Sources: Abivax, ABTECT maintenance Part 1 results (1 June 2026) - supports the four Part 1 50 mg NMSC events; Abivax, ABTECT maintenance Part 2 topline (2026) - supports the 1.37, 0.69 and 0.64 rates and the four Part 2 events; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX's own June 29 safety presentation omits Part 1 alone -- the reconstructed highest-rate dataset. Instead, its NMSC benchmarking slide shows only the integrated program, Maintenance Parts 1+2, and Part 2 alone, all of which produce lower 50 mg rates than placebo-controlled Part 1.

Abivax, June 29, 2026, slide 26 — NMSC exposure-adjusted incidence analysis: Integrated program, Maintenance Part 1+2, and Part 2 only; no Part 1-only analysis shown

NMSCs

All Active Combined NMSC Rates Were Consistent With the Reference Range Across All Three Datasets

Increasing Size and Relevance of Dataset

Integrated UC Clinical Program (Phase 2 + Phase 3 Induction and Maintenance)	Placebo	25 mg	50 mg	All Active Combined	Reference Range Based on Published UC Studies
Total PYs of Exposure	~218	~760	~944	~1,704	-
Observed IR per 100 PY	0.46	0.53	0.64	0.59	0.70 – 1.40

Maintenance (Part 1 + Part 2)	Placebo	25 mg	50 mg	All Active Combined	Reference Range Based on Published UC Studies
Total PYs of Exposure	~147	~274	~438	~712	-
Observed IR per 100 PY	0.68	1.09	1.37	1.26	0.70 - 1.40

Maintenance (Part 2 Only)	Placebo	25 mg	50 mg	All Active Combined	Reference Range Based on Published UC Studies
Total PYs of Exposure	N/A	~132	~288	~420	-
Observed IR per 100 PY	N/A	1.52	0.69	0.95	0.70 - 1.40

Data on File ABX464-103, ABX464-104, ABX464-105, ABX464-106, ABX464-107 and ABX464-108; Patient years rounded to the largest whole number; IR = Incidence Rate; NMSC incidence rates were benchmarked against published IBD and UC literature. Long et al. reported an overall NMSC incidence of 912 per 100,000 patient-years in patients with IBD (0.91 per 100 patient-years). Bencardino et al. reviewed evidence demonstrating increased NMSC risk in IBD and reported an annual NMSC incidence of 733 per 100,000 patients (~0.73 per 100 patient-years). Abbas et al. reported UC-specific NMSC incidence rates ranging from 3.7 to 13.6 per 1,000 patient-years (0.37–1.36 per 100 patient-years) across thiopurine exposure strata. Based on these published estimates, a benchmark NMSC incidence range of 0.7–1.4 per 100 patient-years was used for contextual comparison. Expected cases were calculated as: (incidence rate per 100 patient-years × cumulative patient-years of exposure) ÷ 100.

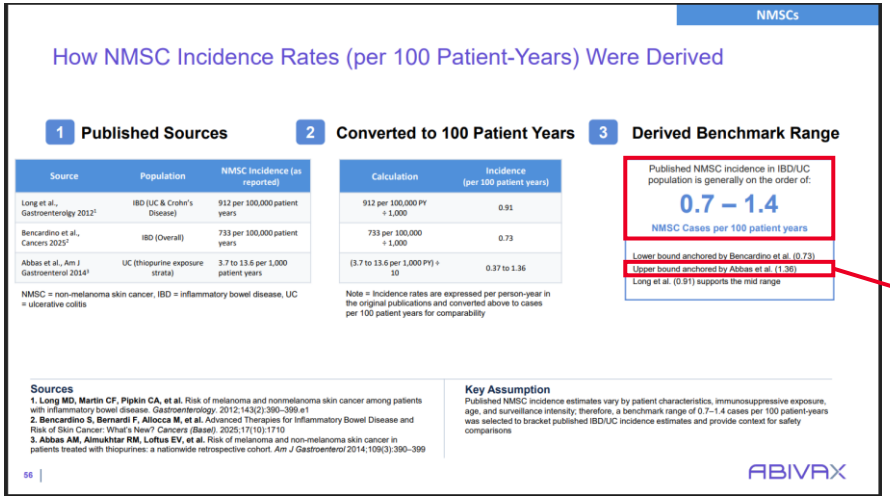
26 | ABIVAX

Sources: https://ir.abivax.com/static-files/b077423a-2be3-423a-aee9-2e6989551f3f?utm_source=chatgpt.com; Abivax, ABTECT maintenance Part 1 results (1 June 2026); Abivax, ABTECT maintenance Part 2 topline (2026); Abivax, integrated summary of safety, ABTECT induction (DDW 2026); Vermeire et al. 2022; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABVX uses a duration-mismatched NMSC benchmark that makes the Phase 3 skin-cancer signal look materially less concerning — Abbas's 5-year thiopurine rate helps set the upper bound for ~1 year of ABX464 exposure, while the same paper reports first-year and thiopurine-naïve rates ~4.7× and ~7.3× below reconstructed Part 1.

Abivax uses Abbas's year-5 NMSC rate to help set the top of its benchmark; Abbas's same dataset reports 0.58/100 PY in year 1 versus our reconstructed Part 1 ABX464 rate of ~2.70/100 PY — ~4.7× higher.

Abivax June 29 deck, slide 56, "How NMSC Incidence Rates (per 100 Patient-Years) Were Derived."



Abbas et al. 2014 — source Abivax cites for thiopurine NMSC rates. Abbas explicitly found that NMSC incidence increased with cumulative thiopurine exposure

Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a nationwide retrospective cohort

Table 3. Incidence rate of NMSC by thiopurine treatment duration

Thiopurines use	*N*	P-Y	NMSC	IR	IRR	95% CI	*P* value	AR	NNH
Unexposed/before use	14,527*	84,980	317	3.7	1				
1st year	3,346	2,584	15	5.8	1.6	0.9–2.6	0.092	2.1	482
2nd year	2,060	1,773	14	7.9	2.1	1.2–3.6	0.005	4.2	240
3rd year	1,537	1,325	11	8.3	2.2	1.2–4.1	0.007	4.6	219
4th year	1,165	1,032	8	7.8	2.1	1.0–4.2	0.037	4.0	248
5th year	914	809	11	13.6	3.6	2.0–6.7	<0.0001	9.9	101
After 5 years	713	1,675	18	10.7	2.9	1.8–4.6	<0.0001	7.0	143

Abivax's June 29 methodology slide sets its NMSC benchmark at 0.70–1.40/100 PY and identifies Abbas's 1.36 fifth-year thiopurine rate as an anchor for the upper bound. Abbas Table 3 shows the same cohort at 0.58/100 PY in year 1 and 0.37/100 PY before thiopurine exposure.

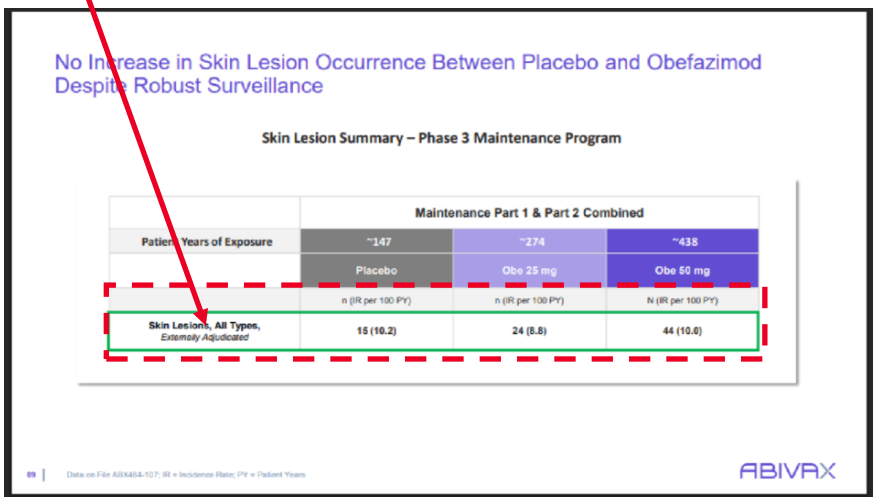
Sources: Abbas et al. 2014; Abivax, ABTECT maintenance Part 2 topline (2026); Abivax, corporate presentation (Data on File), slide 26; Scorpion Capital analysis, modeling, estimates, and literature/publication review

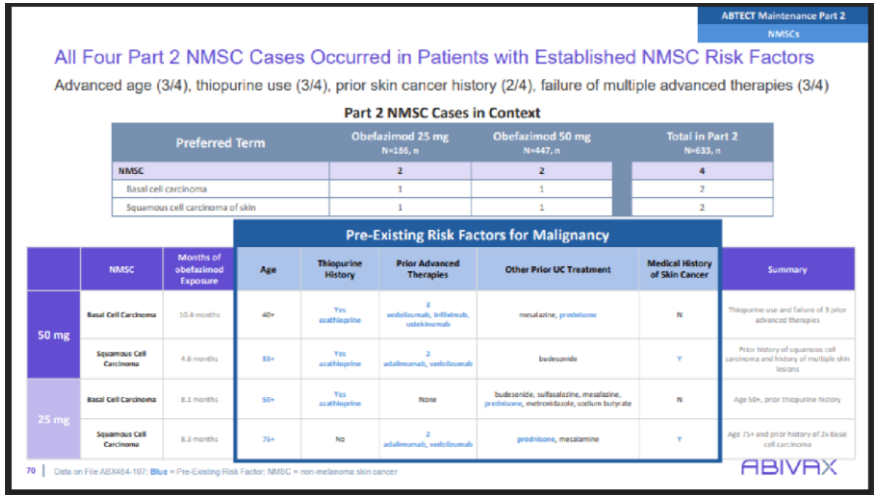
Chapter 19. ABVX's skin-safety disclosures raise disturbing questions of potential under-reporting, inadequate surveillance, and questionable, conflicted central adjudication

ABVX's recent Phase 3 maintenance data reported 68 skin lesions: 4 were identified as non-melanoma skin cancers, while the other 64 were grouped under "skin lesions, all types" with no further breakdown. Based on information from a former ABVX employee involved in safety monitoring, we are concerned as to whether this catch-all category may obscure a substantial number of photosensitivity reactions.

ABVX July 2026 investor presentation

"Skin Lesions, All types"

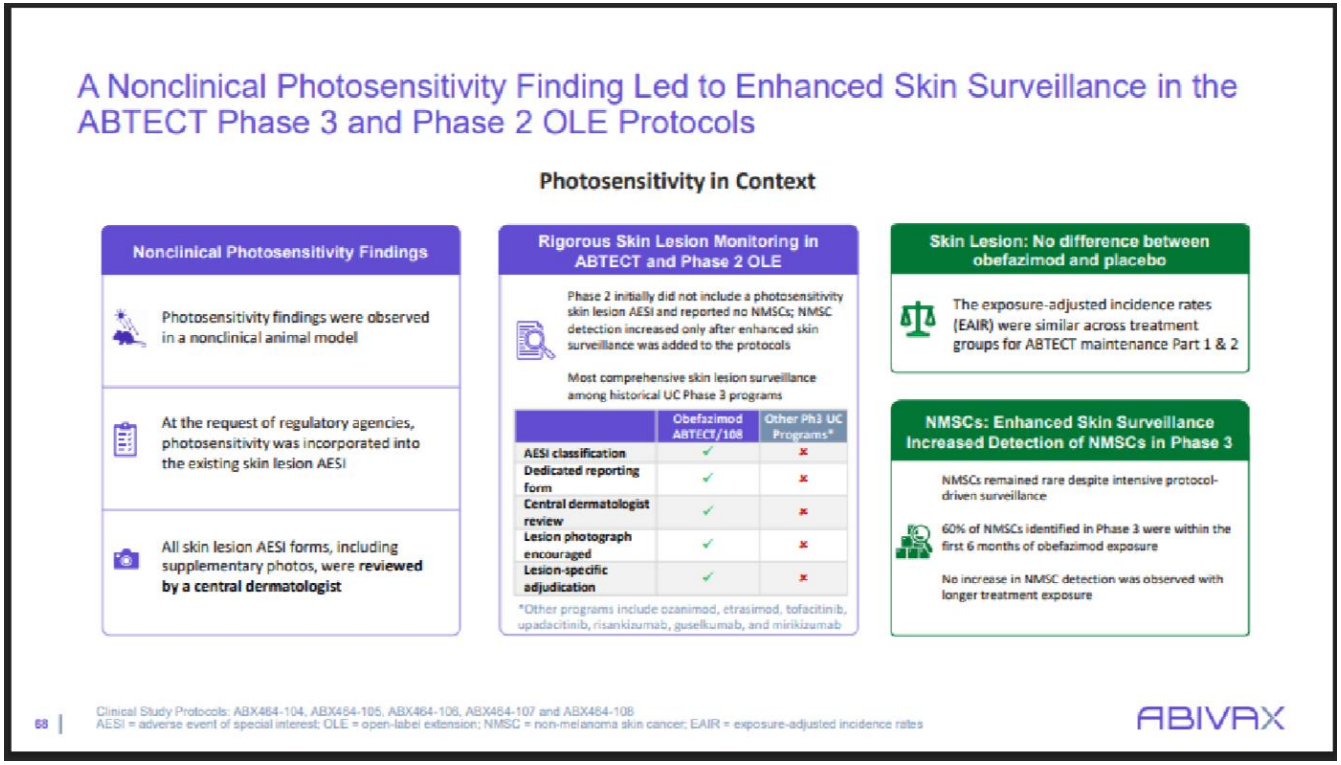




Source: ABVX July 2026 investor presentation, https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d

ABVX's vague lesion breakout is troubling: it identifies just 4 malignancies while leaving dozens of other lesions unexplained, despite protocol-mandated enhanced skin surveillance triggered by a photosensitivity signal. Any failure to disclose photosensitivity reactions would be especially concerning -- given the link between drug-induced photosensitivity and photocarcinogenesis.

ABVX July 2026 investor presentation



A Nonclinical Photosensitivity Finding Led to Enhanced Skin Surveillance in the ABTECT Phase 3 and Phase 2 OLE Protocols

Photosensitivity in Context

Nonclinical Photosensitivity Findings

- Photosensitivity findings were observed in a nonclinical animal model
- At the request of regulatory agencies, photosensitivity was incorporated into the existing skin lesion AESI
- All skin lesion AESI forms, including supplementary photos, were **reviewed by a central dermatologist**

Rigorous Skin Lesion Monitoring in ABTECT and Phase 2 OLE

Phase 2 initially did not include a photosensitivity skin lesion AESI and reported no NMSCs; NMSC detection increased only after enhanced skin surveillance was added to the protocols

Most comprehensive skin lesion surveillance among historical UC Phase 3 programs

	Obefazimod ABTECT/108	Other Ph3 UC Programs*
AESI classification	✓	✗
Dedicated reporting form	✓	✗
Central dermatologist review	✓	✗
Lesion photograph encouraged	✓	✗
Lesion-specific adjudication	✓	✗

*Other programs include ozanimod, etrasimod, tofacitinib, upadacitinib, risankizumab, guselkumab, and mirikizumab

Skin Lesion: No difference between obefazimod and placebo

The exposure-adjusted incidence rates (EAIR) were similar across treatment groups for ABTECT maintenance Part 1 & 2

NMSCs: Enhanced Skin Surveillance Increased Detection of NMSCs in Phase 3

NMSCs remained rare despite intensive protocol-driven surveillance

60% of NMSCs identified in Phase 3 were within the first 6 months of obefazimod exposure

No increase in NMSC detection was observed with longer treatment exposure

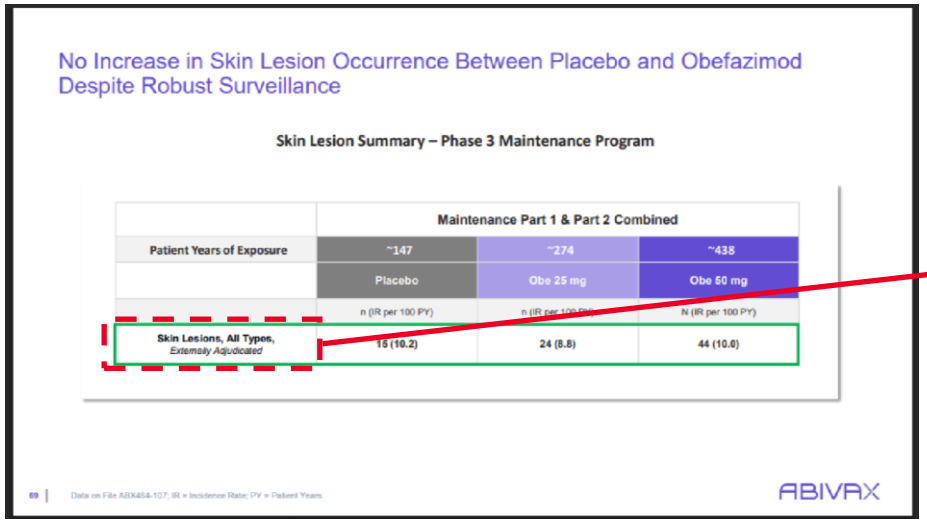
68 | Clinical Study Protocols: ABX464-104, ABX464-105, ABX464-106, ABX464-107 and ABX464-108
AESI = adverse event of special interest; OLE = open-label extension; NMSC = non-melanoma skin cancer; EAIR = exposure-adjusted incidence rates

ABIVAX

Source: ABVX July 2026 investor presentation, https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d

We have substantial concerns at the adjudication process used to determine if skin malignancies/lesions were drug-induced. ABVX indicates cases were "externally adjudicated" rather than "independently adjudicated" – a conspicuous choice of words, given ABVX explicitly called its endoscopy reviewers "independent" and "blinded."

ABVX July 2026 investor presentation states "externally adjudicated" vs. 2022 ABTECT press release indicating "independent, blinded" endoscopy reviews



Skin Lesions, All Types,
Externally Adjudicated

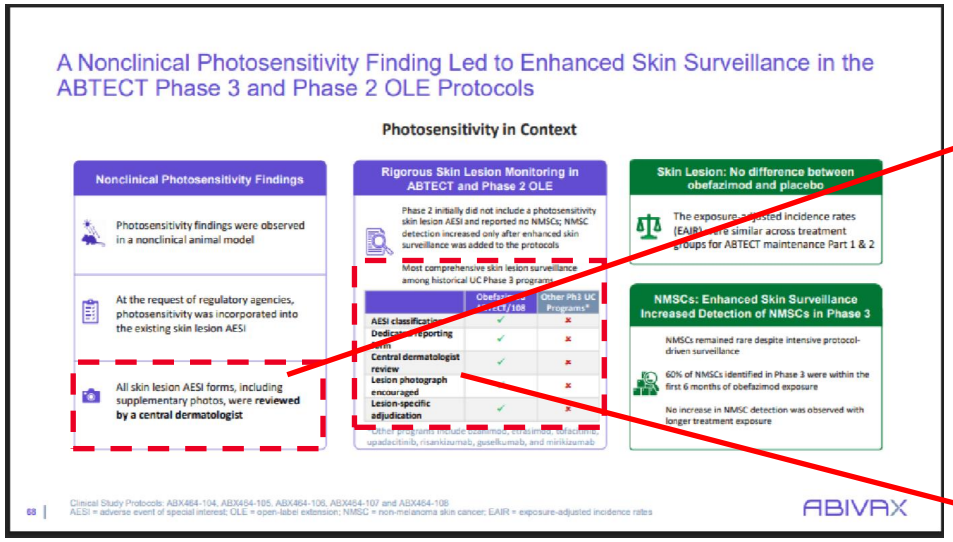
ABIVAX: FIRST US PATIENT ENROLLED IN GLOBAL PHASE 3 PROGRAM WITH OBEFAZIMOD IN ULCERATIVE COLITIS

"These three pivotal studies are all randomized, double-blind, and placebo controlled, ***using independent, blinded review of the videotaped endoscopies."***

Source: ABVX July 2026 investor presentation, https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d; https://ir.abivax.com/news-releases/news-release-details/abivax-first-us-patient-enrolled-global-phase-3-program/?utm_source=chatgpt.com

The company's July 2026 safety presentation makes the dermatologist-review procedure a centerpiece of its argument that there is no meaningful skin signal. It says regulators requested photosensitivity surveillance after the animal findings, that all skin-lesion AESI forms and supplementary photographs were reviewed by a central dermatologist, and contrasts Abivax's supposedly unusually rigorous surveillance with other UC Phase 3 programs.

ABVX July 2026 investor presentation



All skin lesion AESI forms, including supplementary photos, were **reviewed by a central dermatologist**

Most comprehensive skin lesion surveillance among historical UC Phase 3 programs

	Obefazimod ABTECT/108	Other Ph3 UC Programs*
AESI classification	✓	✗
Dedicated reporting form	✓	✗
Central dermatologist review	✓	✗
Lesion photograph encouraged	✓	✗
Lesion-specific adjudication	✓	✗

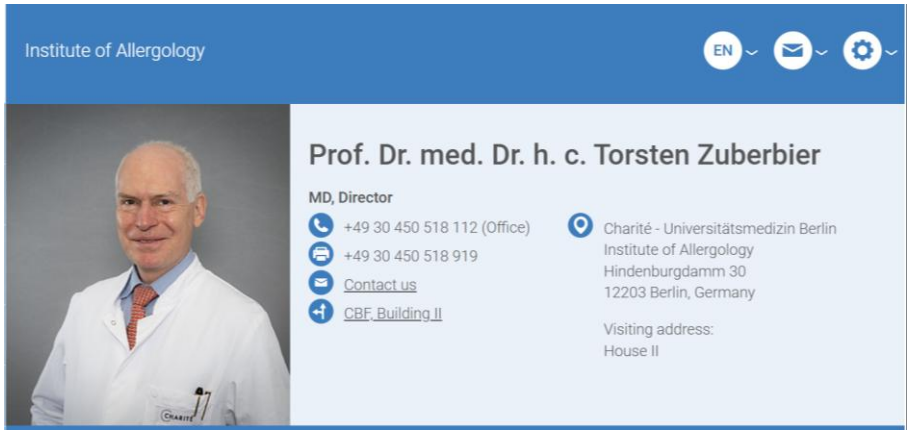
Source: Scorpion Capital consultation calls with experts
Source: ABVX July 2026 investor presentation, https://ir.abivax.com/static-files/ecf996c4-f156-4dac-8e1e-5c4e7cfb8e7d,

An ex-ABVX employee involved in trial safety monitoring told us, per his memory, that he believed the central dermatologist to be Torsten Zuberbier, who appears to be in private practice in Germany. The ex-employee stated "I know he had a relationship with our chief medical officer…they knew one another from a former company or something," referring to ABVX CMO Fabio Cataldi. While we have not been able to independently confirm if Zuberbier was the central dermatologist or his relationship (if any) with Cataldi, we note 2024 and 2025 conflict-of-interest disclosures in two Zuberier papers: "fees for industry consulting were received from Abivax."

Torsten Zuberier bio and conflict of interest statements

Dermatologist allegedly had a pre-existing connection with Cataldi

*"I know that **he had a relationship with our chief medical officer**. They knew one another from a former company or something like that. But I don't think he had like any affiliation with the company. I know that he was **brought on because he knew somebody at the company."** – Ex-Abivax employee closely involved in clinical trials/safety monitoring*



CONFLICT OF INTEREST STATEMENT

Torsten Zuberbier reports honoraria for lectures from Amgen, AstraZeneca, AbbVie, ALK - Abelló, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES Farma, HAL Allergie GmbH, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck Sharp and Dohme, Novartis, Nuocor, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, and Uriach; Fees for industry consulting were received from Abivax, Almirall, ,Bluprint, Celldex, Celltrion, Novartis,

Systems Research Institute and Canadian Institutes of Health Research. T. Zuberbier has received honoraria for lectures from Amgen, AstraZeneca, AbbVie, ALK-Abelló, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES Farma, HAL Allergie GmbH, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck Sharp & Dohme, Novartis, Nuocor, Pfizer, Sanofi, Stallergenes, Takeda, Teva, Union Chimique Belge, and Uriach. Fees for industry consulting were received from Abivax, Almirall, Bluprint, Celldex, Celltrion,

Source: Scorpion Capital consultation calls with experts; https://ifa.charite.de/en/metas/person/person/address_detail/prof_dr_med_torsten_Zuberbier; https://onlinelibrary.wiley.com/doi/10.1002/clt2.70002; https://www.sciencedirect.com/science/article/pii/S2213219825007111?utm_source=chatgpt.com

The ex-safety employee indicated that 20-25 skin-related cases were submitted for review as part of the skin adjudication and signal detection program, and that the files sent included photos and biopsies. The ex-employee added that it was "rare" that biopsies were even done, which raises questions about the rigor of the adjudication – "I remember specifically thinking about that and saying, oh, I wonder why this one's not biopsied."

Ex-employee indicated 20-25 skin-related cases sent to adjudication, mostly from maintenance trial

Q: "You mentioned 20 to 25 skin-related malignancies that were sent to adjudication. Do you remember how many of those were off the Phase 3, the ABTECT? And how many of those were in the Phase 2, the 105, 106? And how many were in 108, that distribution?

*A: "I can infer, but I honestly don't have a concrete answer to that. The **majority of the data was from the long-term extension** versus being from 105, 106." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Ex-employee recalls roughly 25 skin-related cases sent to adjudication, mostly photosensitivity

*Q: "I thought one of the really interesting things you mentioned…**that you recall sending a file of 20 or 25 of these cases —"***

*A: "Correct […] that was part of the **skin adjudication program…the signal detection program**…but it was all retrospective analysis. Maybe out of those 25 from when I had started, there were maybe about four to five that were new…we collected the information, saw the biopsies, whatever relevant patient reports, and then sent all of it collectively with the retrospective and the current ones to the adjudicator." […]*

Q: 'You had about what was it, close to 20 or 25? Do you remember the exact number, or just kind of roughly?"

*A: **"25."***

Q: "There were 25 files, and you said they had photos and other stuff in them?"

*A: "It's typically **patient history and then photos. And if they had taken a biopsy at that time when it was reported, which was rare**, if ever, that was also included." […]*

Q: "How many of these are serious potential skin cancers…I just want to make sure I understand correctly."

*A: "Let's say we had 25 cases. I would say out of those 25, roughly **18 to 20 were something like a rash or something like a photosensitivity reaction**. And the other four to five were something that would have been a potentially benign naevus, a potential squamous cell carcinoma. It was probably about a quarter to an eighth, I'd say. If you had 25 cases, anywhere between three to five potentially should have had biopsies. **I remember specifically thinking about that and saying, oh, I wonder why this one's not biopsied**. I would say anywhere between three to five out of the 25." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

The ex-employee indicated that the majority of the cases sent to adjudication appeared similar to photosensitivity reactions -- "clearly related to sun exposure". When we indicated that we didn't photosensitivity specified in the adverse events table, the ex-employee stated "I am surprised…I am surprised…I really am…I don't know what to say…I didn't realize that wasn't in there."

Ex-employee surprised at lack of detail around photosensitivity

Q: "So, three, four, maybe five cancers. Was it four or was it five, or are you just not sure? It's somewhere in that range? Potential cancers."

A: "I'm just not sure 100% for an actual number. So, I'd like to say three to five…"

Q: "And the ***rest were potential photosensitivity, even if it's a rash? That's why they were sent to you?"***

A: 'Correct. Or solar lentigo, something that is ***clearly related to sun exposure."*** *[…]*

Q: "But what did you think as you were flipping through these?"

A: "I think that there is some potential, obviously, just based on mechanism. It's simply just based on that. If A does B, then B will potentially cause C. ***I'm trying to think whether the photosensitivity was put in the safety tables****. I know that there was a squamous cell, there was a basal cell. It also really depends on how they were adjudicated as being unrelated, not related." […]*

Q: "You're surprised, based on the files you looked at, that these 20, 25 photosensitivity cases are not in the adverse events tables?"

*A: "****I am surprised****, just like I was surprised when you were telling me that we have sites in China that I'd never heard about.* ***I am surprised. I really am. I don't know what to say. I didn't realize that wasn't there."*** *– Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

The ex-employee stated that the substantial number of photosensitivity reactions was well-known at the company: "well, my boss knew...clinical development knew…I have no idea if the chief medical officer knew." When we pressed to confirm that these were in fact photosensitivity reactions, the ex-employee replied that they were large patches exactly where sun exposure would occur – "maybe a three-by-three photosensitivity related thing on somebody's arm or their chest…where they've had clear sun exposure…three centimeters by three centimeters…five centimeters by five centimeters…"

Ex-employee described cases consistent with potential photosensitivity reactions

*Q: "And **how many people were aware of the fact that there were 20, 25 cases of photosensitivity?** Just you? Your boss? Was your whole team aware of this? Or did you email a lot of people at the company? The CMO? Did a lot of people know?"*

*A: "**Well, my boss knew; clinical development knew because they're also involved in the whole adjudication process and how it affects the protocol**, etc. And then I have no idea if the chief medical officer knew." […}*

Q: "And the photosensitivity stuff. Were any of those a serious photosensitivity rash reaction? I know you're not a dermatologist, but what do you remember from some of the images?"

*A: "Well, that's a whole other can of worms because the image quality was absolutely terrible. The dermatologist is looking at these pictures that have been scanned into a medical record and then copied four times, rescanned. They're also dealing with very, very poor quality of data, which is, again, the reason why I was trying to emphasize that what comes off the site is very important to figuring out what's going on. To answer your question specifically, the pictures that I saw were something that you would look at and say, okay, this is maybe a **three-by-three photosensitive-related thing on somebody's arm or their chest or somewhere where they've had clear sun exposure**. It was not anything where it was like full body, full arm, the entire chest, the entire back. It was overall pretty benign in the big scheme of things."*

Q: "But it looked like it was consistent with photosensitivity. Like what? Three inches by three inches? Three centimeters? Three millimeters?"

*A: **"Three centimeters by three centimeters. Five centimeters by five centimeters."***

*Q: **"In an area where they would have had sun exposure?"***

*A: **"Yep."** – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

The ex-employee cast significant doubt on the credibility of the skin-signal adjudication program, stating that the files -- typically photos – may have been sitting around for a year before being sent, despite being flagged by PI's as potentially related to the drug. He further indicated that PI's couldn't even be reached – "they're just not available…difficult to get in touch with these people" – and that the safety reporting was generally "egregious": "they would send us records there were incomplete…records that were wrong…time of the reporting to the sponsor was usually pretty late…."

Skin safety data had allegedly been sitting around; photos flagged for potential association with drug

Q: So, she never sent that data?"
A: "That is the only thing that I can confirm or infer was that was ***not done before I got there."***
Q: "And how stale could that data have been? A couple of years?"
A: "When I looked at it, just very high level, it was ***probably within the past year prior to me starting."***
Q: "And the nature of the data was what? Like photographs and like some kind of case narrative, adverse event narrative?"
A: "It was typically photographs, medical history. One or two of them had a biopsy done, but the ***majority of them were photos."***
Q: "And these were ***investigators flagging it because they thought it could be related to the drug?"***
A: "Yes, that is correct." – Ex-Abivax employee closely involved in clinical trials/safety monitoring

Couldn't get safety data from PI's and/or delays

"The biggest thing was ***trying to get in touch with PIs when we found an issue****, an emergent issue, because* ***they're just not available…it's difficult to get in touch with these people****. I think that was the biggest issue. If we had any type of safety signal that we would want adjudicated, to be reviewed, it took us at least a week or two. And the FDA SUSAR guidelines are 7 to 14 days…" – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Safety monitoring was egregious

"The time in which information was reported from the trial site to the sponsor was one of the biggest variables that I had to deal with because we would get stuff and say, oh, the patient was hospitalized, and then we wouldn't know when. And we'd say, hey, we need to have the records. They would send us ***records that were incomplete. They would send us records that were wrong****. They would send us hundreds of pages of records that we'd have to comb through. That was* ***one of the more egregious things****…the biggest discrepancy that I noticed — just the* ***time of the reporting to the sponsor was usually pretty late."*** *– Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

The questionable quality of safety monitoring/adjudication strikes us consistent with a trial conducted in dubious US and offshore sites. Critically, the ex-employee expressed doubt that skin cancer cases were adjudication via biopsy – "I honestly remember one of the biggest issues was trying to get biopsy reports if they had been done, which was pretty rare…they called them NMSCs, non-melanoma skin cancers…they called them unrelated…it's interesting because I don't think that adjudication was made off biopsies to begin with." Data and image quality were also suspect: "image quality was absolutely terrible…dermatologist is looking at these pictures…scanned…then copied four times, rescanned…also dealing with very, very poor quality of data…:

Ex-employee questions if biopsies were used for skin cancer adjudication

A: "It's interesting because even with the skin adjudication, there were points in time where we were looking at potential non-melanoma skin cancers…there was a basal cell, there was a squamous cell, and there was something else. But ***I honestly remember one of the biggest issues was trying to get biopsy reports if they had them done, which was pretty rare****. That's pre-my-time at Abivax; I wasn't responsible for some of those decisions. I always thought that was kind of interesting because I know that they called them NMSCs, non-melanoma skin cancers. They called them unrelated because there was no direct organ clustering. It's interesting because* ***I don't think that adjudication was made off of biopsies to begin with."***

Q: "You're talking about the ones that they publicly reported in the maintenance data recently?"

A: "Yes. Correct." – Ex-Abivax employee closely involved in clinical trials/safety monitoring

Ex-employee questions if biopsies were used for skin cancer adjudication

Q: "And the photosensitivity stuff. Were any of those a serious photosensitivity rash reaction? I know you're not a dermatologist, but what do you remember from some of the images?"

A: "Well, that's a ***whole other can of worms because the image quality was absolutely terrible. The dermatologist is looking at these pictures that have been scanned into a medical record and then copied four times, rescanned. They're also dealing with very, very poor quality of data****, which is, again, the reason why I was trying to emphasize that what comes off the site is very important to figuring out what's going on. To answer your question specifically, the pictures that I saw were something that you would look at and say, okay, this is maybe a* ***three-by-three photosensitive-related thing on somebody's arm or their chest or somewhere where they've had clear sun exposure****…" – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

Ex-safety employee indicated that melanoma was viewed internally as mechanistic to the drug, and that he was specifically told so – "melanoma was added as a result of the mechanism…I also understand the melanoma component was because of the mechanism of obefazimod…that was determined to be a potential side effect…what they told me when I was reviewing the product and protocol…that, because of the mechanism of action of miR-124 and previous studies…there is a potential for skin issues…photosensitivity, skin lesions…whether it be potential skin cancers, non- melanoma or melanoma…that's kind of what I was told."

Ex-employee states being told that skin-related side effects were related to the drug

*A: "…the **melanoma was added as a result of the mechanism of the drug. That's from what I understand…I also understand that the melanoma component was because of the mechanism of obefazimod."***

Q: "And were you told that in meetings? Was that discussed at the company? Like, we think mechanistically it can cause cancer?"

*A: "**Yeah…somewhere out there, that was determined to be a potential side effect**. And then also through signal detection methodologies…"*

Q: "So, you showed up, and what do they tell you? They said, "Hey [retracted] the drug can cause skin cancer. We know this." What do they tell you because you're the drug safety guy?"

*A: "…**what they told me when I was reviewing the product and protocol is that, because of the mechanism of action of miR-124 and previous studies…there is a potential for skin issues. There's a potential for photosensitivity, skin lesions**. There's never melanoma outright because you can't make that determination unless it's been diagnosed through biopsy and other things. But based on the mechanism, based on signal detection, and based on trends and what was reported, there was a **potential for skin involvement, whether it be photosensitivity, whether it be potential skin cancers, non-melanoma or melanoma. That's kind of what I was told**." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

The ex-employee also indicated that "there was an ophthalmological issue…they were adjudicated as being not related to drug" – but did not provide further detail as to its nature or prevalence.

Various AESI's

Q: What were the AESIs that you guys were concerned about before the trial began? Which ones did you think could be a risk?"

A: "We had cardiac involvement, so any type of cardiac issues: prolonged Q-wave, T-wave. We had potential malignancies. We had liver enzymes, potential DILI, drug-induced liver injury. That was another thing that we were looking at. There was an ***ophthalmological issue…they were adjudicated as being not related to the drug."*** *– Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Dermatologic AESI's – skin malignancies, photosensitivity – "determined to

"The ***AESI category, one of them was dermatologic. As I mentioned, malignancies of the skin****; there was also non-clinical photosensitivity. What we did for that is we just had enhanced surveillance for the ABTECT patients. We partnered with the dermatologist, and then any potential dermatological issue, the trial site would take a photo. They do the full history. Then we'd send it to the dermatologist to adjudicate it. And* ***nine times out of ten, it's patients who are in the sun…it was determined to be not related to the drug because of the dermatologist's decision."*** *– Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

Chapter 20. Undisclosed level of reliance on China – the black hole in ABVX's Phase 3 trial, with alarming red flags for data integrity and fraud; and recent Congressional scrutiny of Chinese sites

China appears to be a key pillar of Abivax phase 3 ABTECT clinical data – a major red flag. Country-level enrollment remains hidden, but regional figures indicate North America P3 enrollment was a mere 10% of total while Asia was 24%, with ~50 Chinese sites listed in the ClinicalTrials.gov record, second only to the US in terms of the number of total sites shown.

ABVX press release Apr 29. 2025 – regional enrollment figures for Phase 2b and Phase 3

Trial Participant Baseline Characteristics: ABTECT Phase 3 vs. Obefazimod Phase 2b

	ABTECT Phase 3	Phase 2b
Study Participants	1,275	252
Baseline MMS (7-9)	65%	71%
Prior Advanced Therapy Failure	48%	48%
Corticosteroids	42%	52%
Geographic Distribution	North America : 10% Western / Central Europe: 22% Eastern Europe:38% Asia:24% ROW: 6%	North America : 1% Western/Central Europe: 33% Eastern Europe: 66%

ABTECT Phase 3	Phase 2b
North America : 10% Western / Central Europe: 22% Eastern Europe:38% Asia:24% ROW: 6%	North America : 1% Western/Central Europe: 33% Eastern Europe: 66%

Source: https://ir.abivax.com/news-releases/news-release-details/abivax-announces-completion-enrollment-phase-3-abtect-trials

The Chinese sites include numerous problematic military facilities -- such as the PLA 900th Hospital – consistently identified as hubs for coercive organ sourcing and transplant tourism. At least five sites have been implicated in executed-prisoner organ sourcing; others allegedly took bribes from drug reps, falsified data, or engaged in other dubious practices.

A few examples of problematic Chinese sites listed in ABTECT ClinicalTrials.gov record; various military hospital trial sites discussed for dubious organ/medical practices per sources below

Guangzhou, Guangdong, China, 510515
Nanfang Hospital of Southern Medical University

Yuexiu, Guangdong, China, 510080
The First Affiliated Hospital of Sun Yat-sen University

Shanghai, Shanghai Municipality, China, 200127
Renji Hospital Shanghai Jiaotong University School of Medicine - West Branch

Changsha, Hu'nan, China, 410011
The 2nd Xiangya Hospital of Central South University

China forcefully harvests organs from detainees, tribunal concludes

Doctor jailed for 17 years over bribery, unnecessary operations

Organ Procurement and Extrajudicial Execution in China: A Review of the Evidence

*"The **military-medical complex became heavily involved in transplant activity** and research; the state began subsidizing a nascent immunosuppressant industry. Transplant waiting times went from many months to just weeks, days, and sometimes hours"*

Source: https://global.chinadaily.com.cn/a/202411/01/WS67242a32a310f1265a1cacb1.html; https://global.chinadaily.com.cn/a/202411/01/WS67242a32a310f1265a1cacb1.html; https://www.nbcnews.com/news/world/china-forcefully-harvests-organs-detainees-tribunal-concludes-n1018646; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3598791; https://www.upholdjustice.org/node/636

Chinese trials are the target of recent Congressional scrutiny. A Jun 2026 letter targeted Pfizer's use of trial data from military hospitals, highlighting suspiciously rapid enrollment, "lack of ethical safeguards" for "informed consent and voluntary participation," and "undue influence" and "overstating efficacy" – noting that Pfizer will halt trials at PRC facilities.

Jun 2026 Congressional letter to Pfizer CEO; other press on Chinese

US clinical trials in China questioned by US lawmakers

US House committee opens investigation into Merck, AbbVie China drug trials

Pfizer Conducted Clinical Trials at Chinese Military Hospitals

JUNE 30, 2026

Select Committee Launches Investigation Into Pfizer's China Work

Chairman John Moolenaar of the Select Committee on China has sent a letter to Pfizer Chief Executive Officer Dr. Albert Bourla asking the pharmaceutical company to provide more information about the company's clinical drug trials in China. Publicly available information on **ClinicalTrials.Gov** already shows the company has developed drugs in clinical trials at Chinese military hospitals, and in Xinjiang, China, where the Chinese Communist Party (CCP) is conducting a genocide of Uyghur Muslims and other minorities.

Source: https://files.constantcontact.com/f0eecb46901/7ce2c65d-4e4f-4c62-81c5-2560781cacbd.pdf; https://chinaselectcommittee.house.gov/media/letters/pfizer-conducted-clinical-trials-at-chinese-military-hospitals; https://www.reuters.com/business/healthcare-pharmaceuticals/us-clinical-trials-china-questioned-by-us-lawmakers-2024-08-20/

The Chinese Food and Drug Administration (CFDA) has flagged systemic fraud and corruption in clinical trials, analyzing 1,622 studies: "most of the data in the studies examined was either incomplete, did not meet the agency's analysis requirements, could not be traced or simply concealed negative results."

Credibility of Chinese clinical trials – various articles

Falsified data in 80% of Chinese clinical trials

A Chinese government investigation has revealed that more than 80 percent of the clinical data used to support trials of new drugs in the past year has been fabricated. According to the report, the results of which were cited by the state-owned China News, the authorities have reviewed 1622 clinical trials awaiting market approval, and it turns out that most of the data in the studies examined was either incomplete, did not meet the agency's analysis requirements, could not be traced or simply concealed negative results. However, this comes as no news to the CFDA, whose top manager already called the

Note To The Chinese FDA: When 80% Of Your Data Is Bad, How Trustworthy Is The Other 20%?

China cracks down on fake data in drug trials

Can we trust clinical trials from China?

Retractions, paper mills, and misconduct, oh my

Source: https://www.pulmccm.org/p/can-we-trust-clinical-trials-from; https://biostock.se/en/2016/10/forfalskade-data-i-80-av-kinesiska-kliniska-provningar/; https://pubmed.ncbi.nlm.nih.gov/28516939/; https://www.forbes.com/sites/benjaminshobert/2016/10/11/note-to-the-cfda-when-80-of-your-data-is-bad-how-trustworthy-is-the-other-20/

Predictably, ABVX sites are plagued by exactly these scandals. At least 7 ABTECT-listed sites rank among university hospitals with the most retracted papers in China. Two Chinese ABTECT sites were the top offenders in the entire country with 48 and 31 retractions each – others each had dozens -- per a 2023 study of retractions across 237 centers. One is Nanfang Hospital, known for historic executed-prisoner organ sourcing.

China medical integrity study – various ABTECT sites listed

Research misconduct in hospitals is spreading: A bibliometric analysis of retracted papers from Chinese university-affiliated hospitals

ABTECT Chinese site	Finding from research integrity summary
Nanfang Hospital, Southern Medical University	**ABTECT contact Side Liu** co-authored a retracted GI/cancer paper. Editors identified multiple apparent image overlaps and concluded the reported data were "unreliable."
Xiangya Hospital, Central South University	**48 retracted papers — highest among 237 Chinese university-affiliated hospitals studied.**
First Hospital of Jilin University	**31 retractions — second-highest** among the 237 hospitals studied.
Shengjing Hospital, China Medical University	24 retractions — all 24 classified as **fake-peer-review cases.**
First Affiliated Hospital of Zhengzhou University	24 retractions — the study identified **data manipulation** as a recurring reason, including 5 cases.
Qilu Hospital, Shandong University	23 retracted papers.
Affiliated Hospital of Qingdao University	16 retractions.

Source: https://www.degruyterbrill.com/document/doi/10.2478/jdis-2023-0022/html?utm_source=chatgpt.com; ClinicalTrials.gov ; Nanfang Hospital organ sourcing, p4 https://www.justice.gov/sites/default/files/eoir/legacy/2013/06/14/china_0894.pdf

ABTECT-listed China sites are a cluster of the worst data integrity and fraud issues in the country – the institutional overlap raises grave doubts about ABVX's entire China dataset. One named ABTECT site investigator/contact, also at Nanfang Hospital, is even the author on a retracted GI paper – an MiR paper, no less -- where editors stated the data is unreliable. He ghosted the journal when contacted.

ABTECT-listed China investigator -- ClinicalTrials.gov record + retraction notice

- **Guangzhou, Guangdong, China, 510515**

Status:	Recruiting
Facility:	Nanfang Hospital of Southern Medical University
Contact:	○ Contact ▪ Side Liu, MD

Original paper says the study was "designed and conceived by Jide Wang, Aimin Li and Side Liu"

Cellular Oncology (2023) 46:237
https://doi.org/10.1007/s13402-022-00768-4

RETRACTION NOTE

Retraction Note: The POU2F1/miR-4490/USP22 axis regulates cell proliferation and metastasis in gastric cancer

Yizhi Xiao[1] · Side Liu[1,2] · Jiaying Li[1] · Weiyu Dai[1] · Weimei Tang[1] · Li Xiang[2] · Wenjing Zhang[3] · Jianjiao Lin[1,2] · Jing Wang[1] · Xiaosheng Wu[1] · Guangnan Liu[1] · Yuyang Liu[4] · Yaying Chen[5] · Huiqiong Zhu[1] · Yusi Wang[1] · Zhizhao Lin[1] · Qiong Yang[1,6] · Tianming Chen[1] · Yong Sun[1] · Aimin Li[1] · Jing Xiong[1] · Jide Wang[1,2]

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Retraction Note: Cellular Oncology (2020) 43:1017–1033
https://doi.org/10.1007/s13402-020-00553-1

The Editors-in-chief have retracted this article because after publication concerns have been raised regarding a number of figures, specifically:

- Figure 3a: the 24h panels for m-NC and i-NC appear to be identical.
- Figure 4f: the AGS and BGC-823 panels for miR-4490/USP22 appear to partially overlap.

The Editors-in-Chief therefore consider the data reported in this the article to be unreliable.

Jide Wang does not agree to this retraction. The editor was not able to obtain a current email address for Tianming Chen. None of the other authors have responded to any correspondence regarding this retraction.

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Source: https://clinicaltrials.gov/study/NCT05507203?a=9&tab=history&utm_source=chatgpt.com; https://link.springer.com/article/10.1007/s13402-022-00768 4?utm_source=chatgpt.com

We have grave concerns about the low-quality countries that comprise the bulk of ABVX's Phase 3 data – more so given the negligible US subgroup and its suspect data, as we detail later. In particular, we question the opaque role of Chinese trial sites, as Asia comprised 24% of P3 patients. We see ~50 China sites listed on ClinicalTrials.gov, with alarming red flags, as we shall cover – yet every ex-employee we interviewed, including those who played senior roles in the Phase 3 trials, indicated they were shut out of China with no involvement or visibility -- despite being involved in Japan and South Korea: "we did have sites in China…this is something even my team had no visibility…that was a big black hole for me…they just told me it's operating differently…they didn't need me or my team there…"

Senior individuals involving in trial oversight had no visibility/oversight of China sites

*A: **"We did have sites in China. But this is something my team had no visibility or not even visibility as to how many** — yeah, we do have sites in China and as to how many they enroll because even the CRO was not so involved there, so **that was a big black hole for me**. I don't know what happened with them."*

Q: "Did you guys try to get visibility? So even your team had visibility into everything but China? Didn't you think that was weird?"

*A: "It was. Again, when you're a contractor, you also have to think about what you want to ask for. But China, no, it didn't seem weird to me because **they just told me it's operating differently. They didn't need me or my team there."***

Q: "And was your team involved in South Korea and Japan?"

A: "Yeah, we had the Japanese."

*Q: "You were **involved in South Korea and Japan, but not in China?"***

A: "Yeah." – Ex-Abivax senior MSL role, via Amplity

Source: Scorpion Capital consultation calls with experts

Ex-ABVX employees were shocked when we asked about China sites, given their roles across international sites including those in Asia. They indicated that functional teams involved in basic site evaluation and investigational visits had no involvement in China – "blowing my mind right now"; "I didn't even know that Chinese sites were on the list because we did no work with them whatsoever…no investigational visits, no PI education, nothing"; "I literally had no clue there was anything going on in China…I never had a single meeting with anybody from regulatory, clin-dev, safety, CMO-level, C-level – any of these guys about anything China-related…did not get brought up in any of the work that I was going the entire time…"

China sites were a black hole – "no investigational visits, no PI education, nothing"

"I had no interaction with any Chinese sites whatsoever…I did not work with any Chinese sites at all. It was purely the US, EU, UK, some parts of South Korea, and some parts of Japan…I honestly don't know anything about the China sites at all…I was involved in all of Europe. The entire EU, the US, and then South Korea as well. ***I didn't even know that Chinese sites were on the list because we did no work with them whatsoever. I didn't have any interaction with our regulatory, clin-dev — any teams regarding anything related to China when I was there at all. No startup, no insight, no investigational visits, no PI education, nothing****." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff expressed surprise/bewilderment that Chinese sites listed on ClincalTrials.gov

*"The fact that you're telling me that right now is very surprising because if you had told me that we had five sites in China, I would have been surprised because, again, I didn't do any work with anything China-related the entire time I was there… I was in Japan. I was involved in Japan…****I literally had no clue there was anything going on in China while I was there. I had no idea. I never had a single meeting with anybody from regulatory, clin-dev, safety, CMO-level, C-level — any of these guys about anything China-related****. The name of that* ***country did not get brought up in any of the work that I was doing the entire time I was there****…the fact that you're telling me there's 50 China sites on clinicaltrials.gov is* ***blowing my mind right now****." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Source: Scorpion Capital consultation calls with experts

Ex-employees stated that China "was not even on my radar…I didn't even know we had trial sites in China…I never received any data from any of those sites…we never had an SIV [site investigational visit]…this is brand-new information…I had no clue….I worked directly with [C-level executive]…and we never had a single – I'll put it like this: the country China was never brought up in any discussions that I had with anybody at any level…we never discussed anything related to China"; "very, very basic due diligence…we didn't do anything with China at all."

International MSL involved with other countries including in Asia was surprised that Chinese sites listed

A: "…[the] medical team was an international team. In terms of the overall team, we had about 10 people overall, but located in Brazil, Mexico, the EU, North America, Korea, Japan — you name it. We were all over the world."

Q: "Were you involved with China as well?"

*A: **"China? I do not believe we had a medical science liaison there."** – Ex-Abivax international MSL, via Amplity*

Key safety staff state they were in the dark China data

***"It was not even on my radar**. That's why I'm saying. **I didn't even know that we had trial sites in China. I never received any data from any of those sites. We never had an SIV**. We didn't even talk to a CRO about monitoring in China. This is **brand-new information**. I had no clue." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff indicated China was never mentioned in any meetings with senior leadership

*"I had literally no idea there were 50 Chinese…this is **brand-new information you're telling me…I worked directly with [redacted – C-level officer/VP]. And we never had a single — I'll put it like this: the country China was never brought up in any discussions that I had with anybody at any level…we never discussed anything related to China**, whether it be clinical trial strategy, monitoring, safety databases, or anything. I did not interact with anybody regarding China at all." – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

Key safety staff state no involvement in site investigation visits

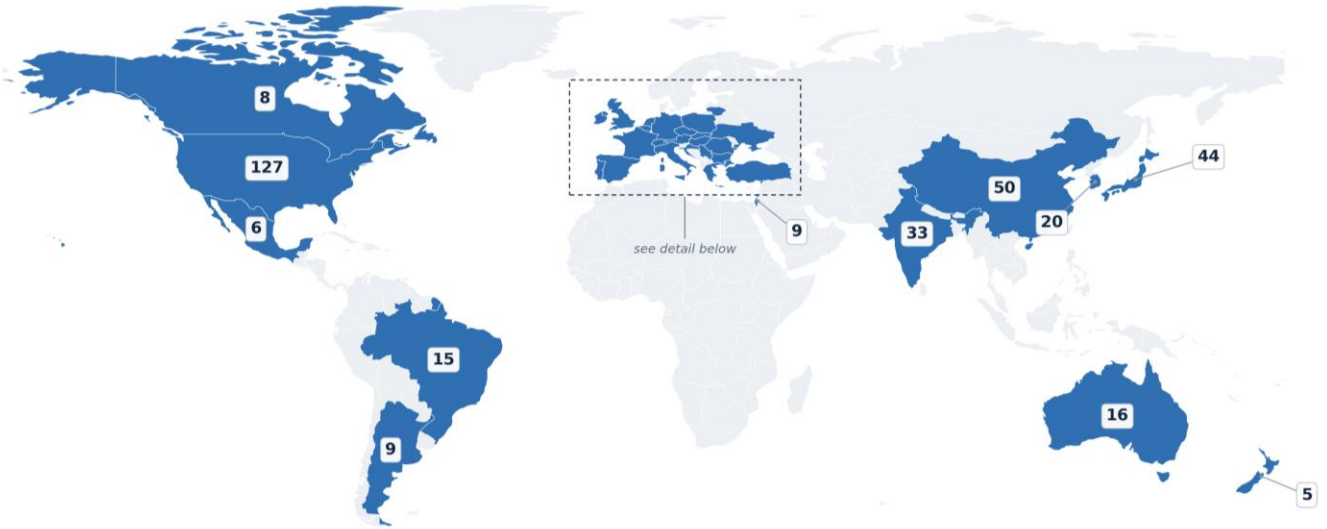
*"A site investigation visit. It's basically to figure out whether a site is capable of running the trial, like the **very, very basic due diligence** that's run in a clinical trial; you do the investigational visit. You make sure that they have all the proper whatever it may be, whether it's like the proper infusion center, the proper pharmacy to dispense the medication, the proper storage — any of that. **We didn't do anything with China at all."** – Ex-Abivax employee closely involved in clinical trials/safety monitoring*

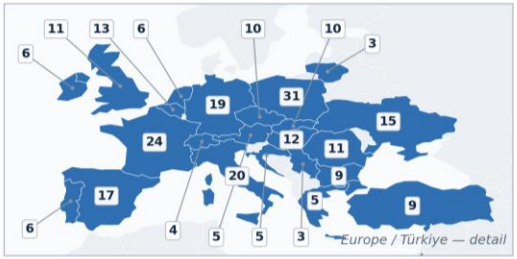
Source: Scorpion Capital consultation calls with experts

Chapter 21. Phase 3 reliance on alarmingly poor US sites and third-tier private practices in questionable areas vs. reputable centers; sites listed in Mexico, India, Ukraine strain credibility.

Beyond China, the ABTECT Phase 3 countries are known for questionable clinical trial reliability and data, with dubious third-tier sites across Mexico, Brazil, India, Turkey, and East European countries like Romania, Bulgaria, and even 15 sites in Ukraine -- we question the credibility of adverse event data collected in a current war zone. Intense FDA scrutiny is inevitable.

ABTECT-1 and 2 clinical trial sites by country per ClinicalTrials.gov locations -- NCT05507203 and NCT05507216





Sites by country

United States	127	Ukraine	15	Ireland	6
China	50	Belgium	13	Mexico	6
Japan	44	Hungary	12	Netherlands	6
India	33	Romania	11	Portugal	6
Poland	31	United Kingdom	11	Austria	5
France	24	Czechia	10	Croatia	5
Italy	20	Slovakia	10	Greece	5
South Korea	20	Argentina	9	New Zealand	5
Germany	19	Bulgaria	9	Switzerland	4
Spain	17	Israel	9	Lithuania	3
Australia	16	Türkiye	9	Serbia	3
Brazil	15	Canada	8		

Source: trial sites listed at https://clinicaltrials.gov/study/NCT05507203?term=abivax&viewType=Card&page=2&rank=12 and https://clinicaltrials.gov/study/NCT05507216?term=abivax&viewType=Card&page=2&rank=11. Map is AI-generated and may contain errors, in particular the trial site totals by country. We refer you to the trial record links for the most accurate source data...

US site quality is the most suspect we've seen at $7B cap – offshore sites look far worse. The lack of tier-1 centers and "real" academic investigators is telling, with heavy reliance on private practices in poorer states and tiny towns – we question their competence/training, trial protocol adherence, data integrity, and endoscopic, safety, and monitoring/reporting standards. Sites below are each roughly an hour from Huntsville, AL and Tampa, FL.

ABTECT trial sites listed on ClinicalTrials.gov – Lakeview Clinical Research (Guntersville, AL), town of 8,500 people; Advanced Research Institute (New Port Richey, FL)







Source: Images from Google Maps after looking up trial sites on ClinicalTrials.gov

Many sites have vague, dubious names and look like sketch "CRO's" in low-income areas – lots of strip malls, no websites we can locate, stock or AI-generated images. Sanchez Clinical Research is typical -- in a derelict Miami strip mall next to a pawn shop with Spanish signage -- yet lists numerous trials and calls itself a fast-growing "Miami research center leader."

ABTECT sites listed on ClinicalTrials.gov – Sanchez Clinical Research (Miami, FL)







Source: Google Maps images; ClinicalTrials.gov; https://sanchezmr.com/departments

We did not evaluate every ABTECT site and note a few academic ones (Indiana, Nebraska, Alabama, Michigan), but the general lack of academic sites in large states or metro areas (NY, MA, TX, FL, PA, etc) associated with KOL's and centers of excellence is a red flag for a purportedly blockbuster drug. The sites below are more typical: Fargo, ND; Baytown, TX; Tampa, FL.

ABTECT trial sites listed on ClinicalTrials.gov







Source: Images from Google Maps after looking up trial sites on ClinicalTrials.gov

The ABTECT foreign sites are troubling. Searches on individual centers listed reveal endless red flags, scandals, and misconduct. A tertiary Mumbai hospital, King Edward Memorial, is typical – patients littered on floors, and a published study that documented recurring informed consent violations at the site, "investigators" who don't understand trial protocols, improper adverse event monitoring, protocol deviations, etc.

ABTECT sites on ClinicalTrials.gov – King Edward Memorial Hospital, Mumbai, India; clinical trial lapses documented in Indian Journal of Medical Ethics, https://doi.org/10.20529/IJME.2019.042









Source: ABTECT trial sites shown on ClinicalTrials.gov; https://doi.org/10.20529/IJME.2019.042; images from Google Maps record for KEM Hospital, Mumbai, India

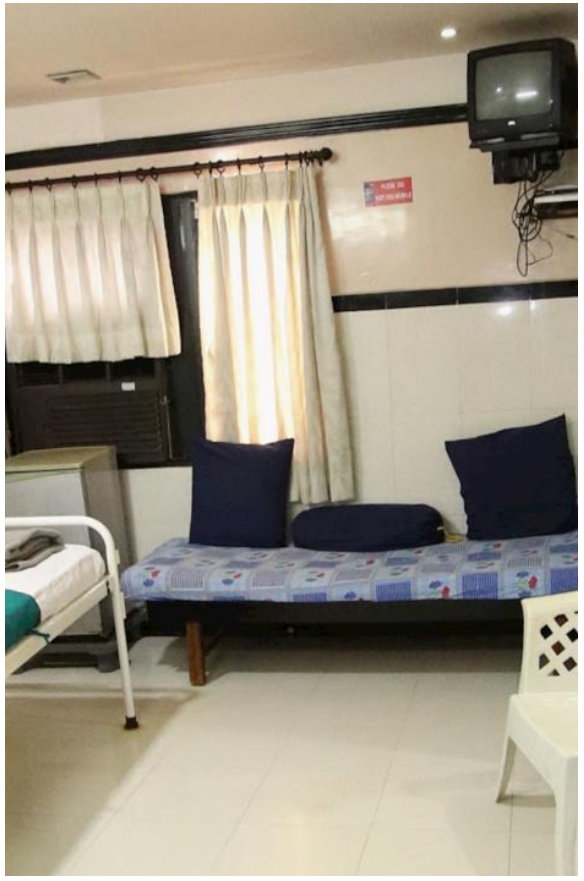
“Sushrusha” Hospital in Ahmedabad, India, looks equally primitive. Google reviews are alarming: “Ahmedabad’s most useless hospital…you bring your fellow patient here, you will take him home dead”; “these are not experienced docter [sic]…get out of here as soon as possible”; “her stacher [sic] banged on the floor on the head…very irresponsible person.”

ABTECT sites on ClinicalTrials.gov -- “Sushrusha” Navneet Memorial Hospital in Ahmedabad, India







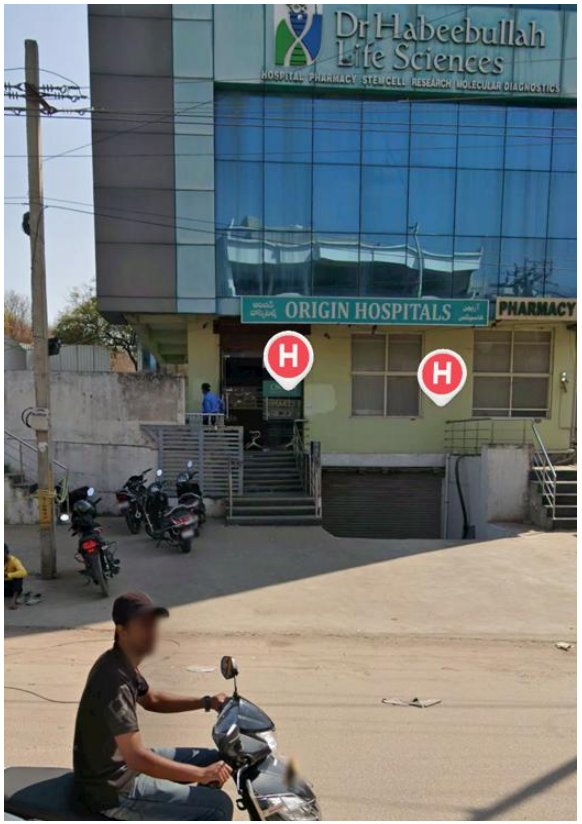


Source: Google Maps and reviews https://maps.app.goo.gl/HfTNSt233wf1mZw28

Origin Hospital in Hyderabad, India – which seems to be known as "Dr. Habeebullah Life Sciences" per the signage – strikes us as similarly suspect and lacking in credibility as a clinical trial facility. Google reviews are just as frightening: "I'm sharing this to strongly warn others…even in an emergency please avoid this hospital…just exploitation…the lack of ethics, transparency, and professionalism is alarming."

ABTECT sites on ClinicalTrials.gov -- Google Maps photos for Origin Hospital in Hyderabad, India



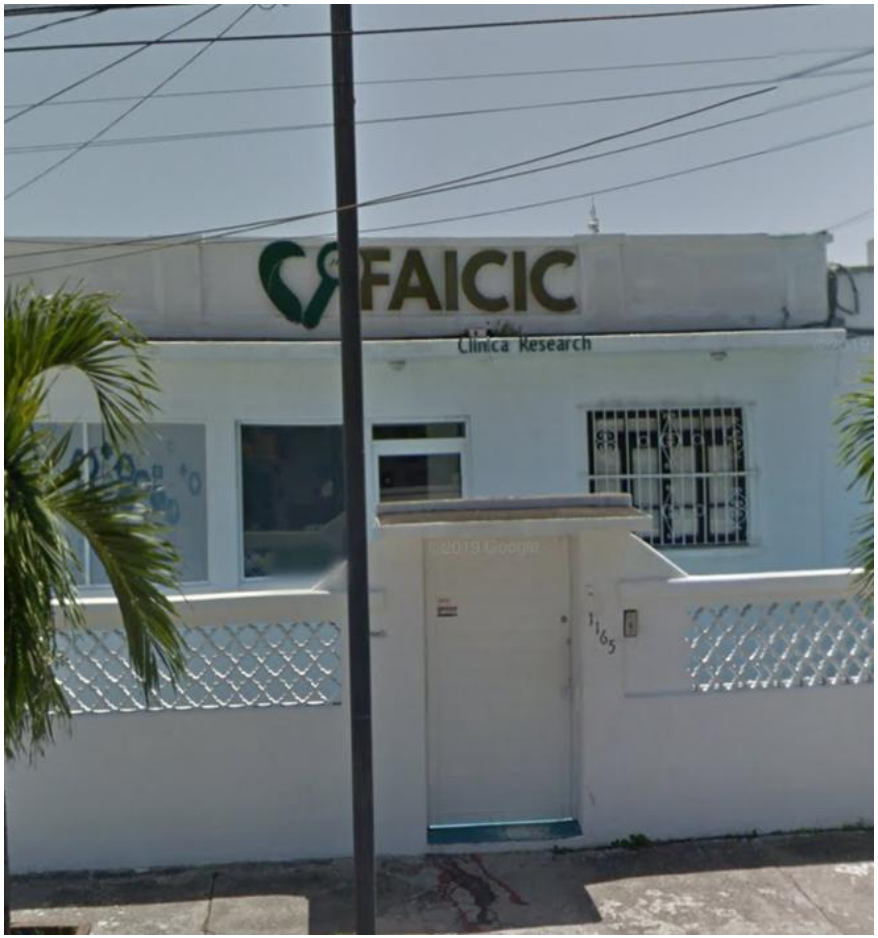




Source: Google Maps https://maps.app.goo.gl/vFzS6tNSmXELLKK2A

The Mexico trial sites look as preposterous as the India ones. We see no facilities in tier-1 metros like Mexico City – the ones listed are in remote, peripheral areas like Veracruz, 250 miles away; Iraputo; and Monterrey. The FAICIC clinical site in Veracruz is shown below.

ABTECT sites on ClinicalTrials.gov -- FAICIC S. de R.L. de C.V. in Veracruz, Mexico



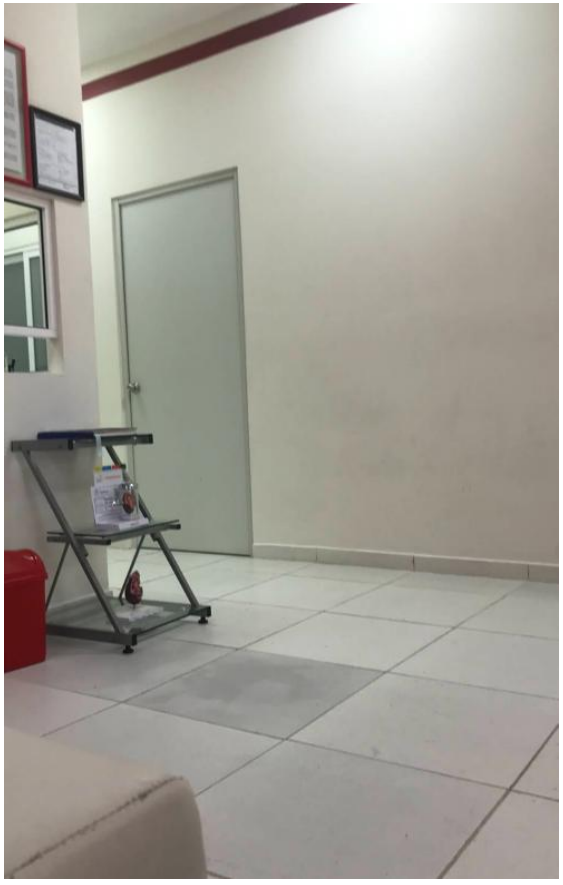


Source: ClinicalTrials.gov, Google Maps images

Another trial site in Veracruz, Mexico, is a short walk from the previous one, making us wonder if they're affiliated with the same "investigator." We question why these random private practice facilities are the best Abivax could find in Mexico -- we don't see a single academic center listed on ClinicalTrials.gov.

ABTECT sites on ClinicalTrials.gov -- Sociedad de Metabolismo y Corazon S.C in Veracruz, Mexico





Source: ClinicalTrials.gov, Google Maps images

ABVX data is very dependent on Eastern Europe -- 38% of ABTECT patients. Poland is key -- we count 31 sites, top 5 for Phase 3, more than any Western Europe country. Polish sites have a documented history of red flags. A recent FDA/CDER warning letter doubted the "reliability of the data and the integrity of your study conduct" at a Phase 3 site. Polish government audits have uncovered major irregularities, even "illegal and unreliable activities."

Polish clinical trials – studies indicating serious deficiencies

Failures in Clinical Trials in the European Union: Lessons from the Polish Experience

Findings of the Supreme Audit Office of Poland (the NIK) Audits

In the conclusion of the first report, the authors wrote: „In the field of clinical trials the NIK found uneconomical, illegal and unreliable activities as well as the potential to expose patients to harm […] Pharmaceutical companies […] have more influence in conducting, financing and financial control of clinical research than public

Controversy over conducting clinical trials in Poland

Source: https://link.springer.com/article/10.1007/s11948-012-9400-9; ; FDA warning letter https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/konrad-rejdak-md-phd-671405-05292024; https://pubmed.ncbi.nlm.nih.gov/31974090/; https://www.termedia.pl/Controversy-over-conducting-clinical-trials-in-Poland,100,26561,1,1.html

Exterior/interior images of listed ABTECT sites in Poland, Bulgaria, and Romania strike us as consistent with published concerns.

ABTECT sites on ClinicalTrials.gov -- Poland, Bulgaria, Romania







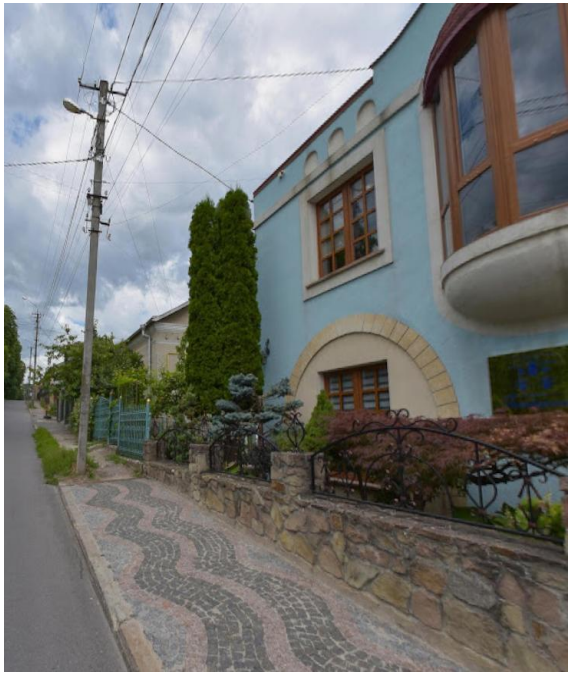




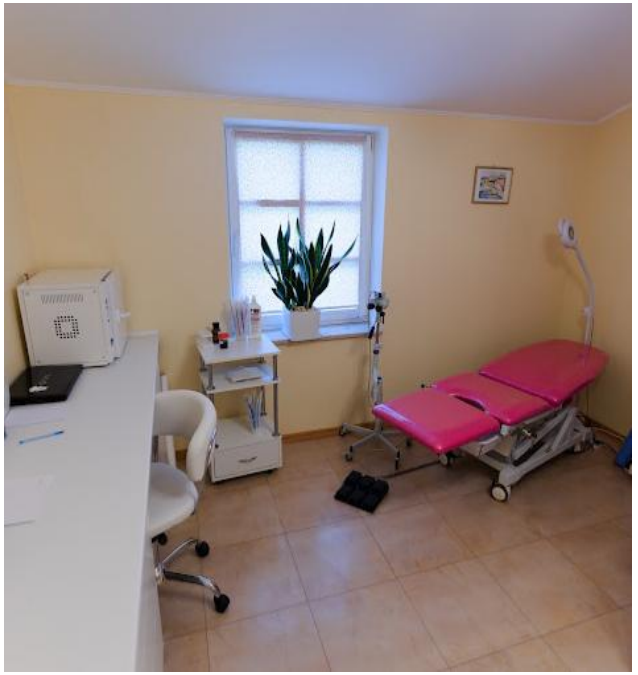
Source: Google Maps images for MC Medica Plus, Bulgaria (far left), DCC 'Sv. Pantaleymon, Bulgaria (2 rooms on bottom right); Nowe zdrowie-CK, Kieltucki i wspolnicy sp. j., Poland (top right); Spitalul de Oncologie Monza, Romania

We count 15 sites listed in Ukraine – enrolling during a war. A recent study noted a collapse in clinical trial reliability since the war began. FDA/EMA precedent doesn't appear to be in ABVX's favor. The FDA recommended excluding Ukraine patients in a recent GI phase 3 trial, and the EMA has warned that wartime data may be unsuitable for regulatory reliance.

ABTECT sites on ClinicalTrials.gov – Ukraine; EMA guidance on Ukraine wartime data







Impact of the war in Ukraine on methodological aspects of ongoing clinical trials - Scientific guideline

Source: ClinicalTrials.gov; Google Maps images -LLC Medical Center The Clinic of Hospodarskyy, Ukraine; NDA indicating negative Ukraine war impact https://cdn.clinicaltrials.gov/large-docs/30/NCT03926130/SAP_002.pdf?utm_source=chatgpt.com; https://www.ema.europa.eu/en/impact-war-ukraine-methodological-aspects-ongoing-clinical-trials-scientific-guideline

Although ABVX used IQVIA – a well-known CRO -- an ex-executive and other former employees indicated "we got the C team" and "shitty team" at IQVIA" and that trial oversight was a farce, with low-quality, dubious sites that never should have been selected: "lack of oversight…the site selection mis…a calamity of errors"; "our partnership with IQVIA...we had a lot of problems with our CRA's [contract research associates]" interfacing with sites.

CRO was "a calamity of errors"

"They engaged IQVIA, but they kind of just let IQVIA go. You either get A teams or B teams or C teams. And I think ***we got the C team for IQVIA. And so it was a myriad of issues: lack of expertise, lack of oversight, potentially the site selection mix****…I don't think that they knew that they were getting the shitty team at IQVIA. But I also don't think that the team was really actively managing either. It was a* ***calamity of errors."*** *– Ex-Abivax senior executive*

"lot of barriers to recruitment"; issues with CRO's

*"We had a lot of different barriers with recruitment…one of the biggest barriers…****was just kind of a general distrust with a new mechanism of action****, given that we already have quite a few agents on the market as it is. A lot of patients were just kind of hesitant to sign up and make that switch…another big thing, honestly, was our partnership with IQVIA. We had* ***a lot of problems with our CRAs and a lot of them not being really up to speed within the IBD space****, the ulcerative colitis space…" – Ex-Abivax MSL*

Source: Scorpion Capital consultation calls with experts

Ex-employees were “pretty sure” ABVX turned to India and sites in places like Ukraine where sites failed to follow basic standards – “not tracking in with their patients…weren’t entering data…not appropriate…following guidelines….”

Ex-executive was “pretty sure” that the trial enrolled patients in India

A: “Eastern Europe definitely was a large driver of the trial for sure. And then they did have a subset of patients in Asia. We did not consider Brazil at the time, but I know India was part of the mix as well.’

*Q: “And did they **go to India?”***

*A: “I'm **pretty sure they did. Yes.”** – Ex-Abivax senior executive*

Serious compliance/protocol adherence issues at Ukraine sites

*“It might have been one of the Ukraine sites that was not doing a good job entering complete patient data…I heard frustration expressed, like, oh my God, someone was not doing a great job overseeing this site. **They were not tracking in with their patients. They weren't entering data. This is not appropriate. More so, in the sense that this site wasn't following guidelines**; they weren't entering data.” – Ex-Abivax executive*

Source: Scorpion Capital consultation calls with experts

Medical science liaisons (MSL's) interfacing with investigators expressed skepticism of questionable trial sites in random, small towns. An MSL noted that a Houston KOL at a "major institution" recruited almost no patients, while a nearby town with "a few thousand" population was prolific: "the biggest enroller I had…was a site down in Texas…a community hospital…a really small town…I was surprised at how they even got the numbers that high." Another MSL described a small town hours from Toronto – "only site in hundreds and hundreds of miles…not the most reliable of patients there…in the middle of nowhwere…interesting to see that they were a clinical trial site in the first place…really quite remote…."

One of the largest enrollers was a community hospital in a tiny town outside of Austin; major centers/KOL's had "pretty scarce" trial enrollment

*"I think the **biggest enroller I had — there was a site down in Texas**. It's been a while now. I want to say they had over 10 patients, for sure…this was a **community hospital…it was a really small town. I was surprised at how they even got the numbers that high** because it was a pretty small town…I would say maybe a few thousand [population]…one of the major institutions we had was in Houston. We had a PI. Her name is Dr. [redacted]. She is actually a global KOL. It was kind of great having her come aboard on our trial and be a PI. However, her recruitment was pretty scarce. I think we might have gotten two patients out of her through my duration there." – Ex-Abivax MSL*

Remote, tiny town in Ontario "in the middle of nowhere"; "really quite remote"

*"…there was another one in northern Ontario, a much smaller site. This was the **only site in hundreds and hundreds of miles**. So, you're getting anyone and everyone to come through, maybe not the most reliable of patients there…maybe a few thousand [people], but still a much smaller town. It's kind of in the **middle of nowhere**…a couple hours [outside of Toronto]…kind of interesting to see that they were a clinical trial site in the first place…I was in the middle of nowhere and not sure it was worth my time to see the site…I think it was part of a mall…**really quite remote "** – Ex-Abivax international MSL, via Amplity*

Source: Scorpion Capital consultation calls with experts

MSL's criticized the trial sites as in poor areas with Spanish-speaking, Medicaid populations that "definitely just should not have been a part of the trial" – "in the Florida region, definitely…Texas as well…heavy Hispanic population"; "Miami and Orlando…smaller operations….the receptionist is going to greet you in…Spanish…that kind of place…"; "our biggest grievance was site selection…I don't know how IQVIA selected a lot of these sites"; "some of the PI's I encountered…you can tell this guy isn't even that well-versed in UC in general….some of these sites should not have been selected, just not having confidence in some of these PIs…"

Florida/Texas sites were poor, Spanish-speaking Medicaid populations; "some of those sites definitely just should not have been a part of the trial"

*A: "Florida. Let me go back to the sites. There were a number of sites, mostly in **Miami and Orlando, in that region…some of them were smaller operations**…It was mostly a **Spanish-speaking population**…I went there. I mean, the receptionist is going to greet you and **talk to you in Spanish before English. That kind of place…:It was a lower socioeconomic background**. It was kind of mostly the population within that Miami area "*

Q: "And was that consistent with the other centers? It was basically lower-income people that they were just kind of jamming into the trial?"

*A: **"I can say that in the Florida region, definitely…Texas as well…heavy Hispanic population**. But more to the point of kind of lower-income Medicare/Medicaid population […] even the MSLs and across the board on the team, **our biggest grievance was just the site selection. Like, I don't know how IQVIA selected a lot of these sites, but some of those sites definitely just should not have been a part of the trial."** – Ex-Abivax MSL*

Highly questionable sites that should not have been selected; "not having confidence in some of these PI's"

Q: "And primarily because they weren't enrolling, or just because they were careless and had poor quality control?"

*A: "I think one and the same. A lot of these sites were not enrolling, but that's because they are **not sites that are really of this caliber to conduct these kinds of trials... I don't know how IQVIA goes about actually selecting these sites**…some of the PIs I encountered and some of the personnel there, it's like, hey, you can tell that this guy probably **isn't even that well-versed in UC** in general […] CRAs, I mean, they kind of were **echoing some of what we were saying, like, hey, some of these sites should not have been selected, just not having confidence in some of these PIs."** – Ex-Abivax MSL*

Source: Scorpion Capital consultation calls with experts

An MSL described a Texas investigator's conduct as an example – a site that had been flagged in the past but was still selected for the ABVX trial, where the MSL suspected the site was seeking improper payment: "…even the CRA had told me that she actually raised concerns in the past about this sites…older gentlemen…didn't look like he gave two shits"; "they're disguising it under recruitment…but no, they just want money…most of it would have been pocketed, in my opinion"; "they had nothing in order…paperwork was just all over"; "I actually reported that internally…hey guys, I don't know how this site got selected…but it doesn't feel right…."

Site that didn't give "two shits"; flagged previously by CRO; allegedly trying to hustle for money

*A: "That one trial in **Texas where even the CRA had told me that she actually raised concerns in the past about this site**. That site in Texas, this guy, he was an **older gentleman; he just didn't look like he gave two shits about what's going on**. He's just like, "Yeah, I'm trying to recruit. We got the flyers." He's just there for the check. And then his coordinator was all about getting more money for advertising. And he's like, we want to put this on TikTok. We want to put this on this and that, and just saying a lot of outlandish things that I'm just like, **they just want money, and they're disguising it under recruitment. But no, they just want money**. And I don't think we're going to see a lot of success with this site here.I,"*

Q: "They were just hustling you for social media, saying it was for money, but they're just going to pocket it. That was your sense?"

*A: "I feel like they would have maybe spent a little on social media, but **what they were asking for, most of it would have been pocketed, in my opinion."** – Ex-Abivax MSL*

Trial sites with red flags – asking for social media funding; disorganized; "I actually reported that internally"

*"…just outside of — I believe that was Dallas — and you can tell that he had no interest in the trial. It seems like they're just there to collect the check. They set up the trial, they're excited to be there up front. But as I was inheriting Texas and I went to go visit, I mean, **they had nothing in order. Paperwork was just all over**. Kind of talking to him, engaging the progress within the trial, protocol questions, and just making sure everything is copacetic with them, you can tell he's very far removed from the day-to-day. And then even his research coordinator, he was a little bit better, of course, but you can still tell that they were not really interested in bringing in patients. They were more interested in, hey, we need more money for advertisements. We need to advertise on Facebook. We need to get on TikTok, they mentioned, and just like looking for, hey, how much more money can we get to put these ads up? And **I actually reported that internally. I said, hey guys, I don't know how this site got selected or what's going on, but it doesn't feel right.."** – Ex-Abivax MSL*

Source: Scorpion Capital consultation calls with experts

Chapter 22. Obefazimod's purportedly blockbuster Phase 3 efficacy is remarkably mediocre – with troubling endpoint manipulation, lack of dose-response, and other inconsistencies and red flags

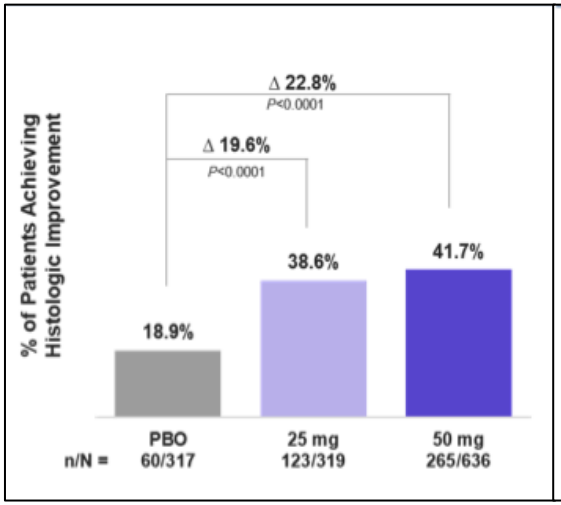
ABX464's clinical efficacy is underwhelming versus approved UC therapies. Despite a headline 77% drop in fecal calprotectin (FCP, an intestinal inflammation biomarker), histologic remission was an unremarkable 9.3%; there is no coherent dose response, clinical and endoscopic efficacy is middling -- and key histology tests failed, were dropped, or were simply not reported.

- **FCP and tissue histology tell very different stories.** At 50 mg, fecal calprotectin falls 77% by week 8, yet histologic remission reaches only 9.3% — just 4.3 points above placebo. Most treated patients therefore still have histologic evidence of mucosal inflammation despite the dramatic luminal biomarker response.
- **Even ABVX's broader "histologic improvement" endpoint leaves substantial inflammation behind.** At 50 mg, only 41.7% meet Geboes ≤3.1, meaning 58% fail the endpoint; the threshold itself still permits neutrophils in up to 5% of crypts. Roughly 91% fail the stricter histologic-remission definition.
- **The 77% FCP reduction is not reflected in the other Phase 3 endpoints.** Endoscopic and histologic responses move far less, and the pattern does not show a coherent dose response. Histologic remission is actually lower at 50 mg than at 25 mg: 9.3% versus 10.7%.
- **Phase 2b showed the same absence of dose response.** Across a fourfold dose range, 25, 50 and 100 mg each improved partial Mayo by about 1.8 points at week 4. After week 4, most of the additional improvement came from continued placebo recovery rather than a growing drug effect.
- **Against approved UC therapies, ABX464 does not stand out.** At 50 mg it is at the low end on strict histo-endoscopic remission, the lowest of the matched HEMI readouts we reviewed, and roughly middle-of-the-pack on clinical remission and endoscopic improvement.
- **The Phase 2b histology record raises additional questions.** Robarts scores are missing for 12–19% of endoscoped patients at week 8, with a larger gap in the 50 mg arm at week 16. Robarts also failed ABVX's prespecified 50 mg statistical gate; it was later removed from Phase 3. Nancy was prespecified and collected but not reported, while Geboes — the least reproducible of the three indices in published inter-rater comparisons — became the Phase 3 histology measure.
- **Mass action and AhR effects provide an alternative explanation for the clinical results.** The FCP–histology disconnect and weak dose-response pattern are consistent with the mass-action and AhR effects developed elsewhere in this report, but our central point does not depend on that explanation: the reported clinical efficacy itself is unremarkable.

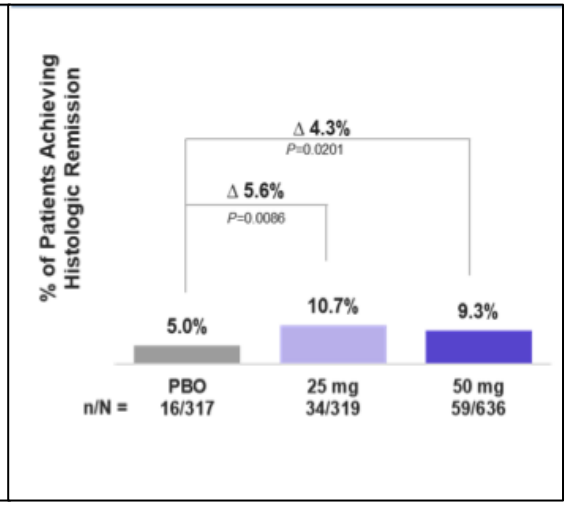
ABVX reports 41.7% “histologic improvement” at 50 mg, but only 9.3% achieve histologic remission — because the broad improvement endpoint still allows residual inflammation. In other words, 58% fail even the broader “histologic improvement” threshold, while 90.7% fail the stricter remission endpoint, including its inflammatory and tissue-damage criteria.

Pooled ABTECT-1/2 Phase 3, week 8 — histologic improvement vs. histologic remission (Magro et al., ECCO 2026 P0922)

Geboes ≤3.1 — Histologic improvement



Geboes <2.0 — Histologic remission



- **The endpoints use very different thresholds.** “Histologic improvement” (Geboes ≤3.1) still permits neutrophils in <5% of epithelial crypts and allows lower-grade inflammatory abnormalities to remain.
- **Histologic remission (<2.0) is much stricter:** no neutrophils in the epithelium or lamina propria, no increased eosinophils, no crypt destruction, and no erosions, ulcerations or granulation tissue.
- **At 50 mg, 41.7% met improvement but only 9.3% achieved remission.** The 32.4-point gap shows how much the reported efficacy depends on the histologic threshold; the aggregate data do not identify which criterion caused each patient to fail remission.

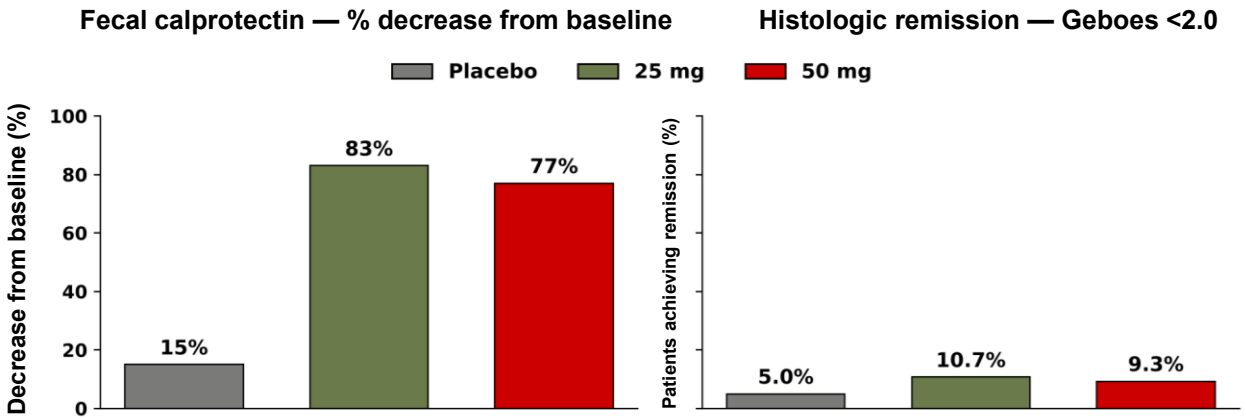
Methodoogy. Pooled ABTECT-1/2 Phase 3 induction, Week 8. Patients received obefazimod 50 mg (n=636), 25 mg (n=319), or placebo (n=317). Histologic improvement was defined as Geboes ≤3.1; histologic remission as Geboes <2.0. The stricter remission definition requires absence of neutrophils in epithelial crypts and lamina propria, no increase in eosinophils, no crypt destruction, and no erosions, ulcerations or granulation tissue. Missing Week-8 outcomes and intercurrent events were handled by non-responder imputation. Bars are sponsor-reported results. Source: Magro et al., ECCO 2026 P0922; NCT05507203; NCT05507216.

Sources: Magro et al. 2026; https://www.abivax.com/wp-content/uploads/abivax-poster-P0922-Magro.pdf; NCT05507203; NCT05507216; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Against the stricter histologic-remission benchmark, the headline 77% FCP reduction does not translate into tissue remission. At 50 mg, only 9.3% achieve histologic remission — a striking disconnect between the luminal biomarker and biopsy evidence of disease clearance.

FCP and histology measure different compartments. Fecal calprotectin reflects neutrophil-derived protein reaching the intestinal lumen, while biopsy histology assesses inflammatory cells and tissue damage remaining in the mucosa. At 50 mg, FCP falls 77%, but 90.7% of patients still fail the stricter histologic-remission endpoint.

Pooled ABTECT-1/2 Phase 3, week 8 — fecal calprotectin reduction vs. histologic remission (Siegmund et al., ECCO 2026 DOP057; Magro et al., ECCO 2026 P0922)



Scorpion Capital reconstruction from sponsor-reported pooled ABTECT-1/2 data. FCP percent reductions are calculated from Siegmund et al., ECCO 2026 DOP057; histologic-remission rates reproduce Magro et al., ECCO 2026 P0922

- **FCP shows a dramatic headline response:** mean fecal calprotectin falls from 3,764 to 870 µg/g at 50 mg by week 8, a 77% reduction. The 25 mg arm falls 83%; placebo falls 15%.
- **Tissue remission remains low:** histologic remission is 9.3% at 50 mg versus 5.0% on placebo — only a 4.3-point absolute difference — and is actually lower than the 10.7% rate at 25 mg.
- **The two readouts therefore tell very different stories.** A large fall in a stool biomarker does not demonstrate comparable resolution of mucosal inflammation on biopsy
- **Our interpretation:** One possible explanation is impaired neutrophil transit from mucosa into the lumen, which could lower FCP without equivalent tissue clearance. The clinical data demonstrate the compartmental disconnect; they do not by themselves establish this mechanism.

Sources: Siegmund et al., DOP057, ECCO 2026; Magro et al., DDW 2026. Pooled ABTECT 1 & 2, week 8; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Oddly, the 77–83% FCP reduction is far larger than the endoscopic and histologic response rates, while Phase 3 shows no coherent dose response — histologic remission falls from 10.7% at 25 mg to 9.3% at 50 mg.

Pooled ABTECT-1/2 Phase 3, week 8. FCP is percent reduction from baseline in a continuous stool biomarker; the other four endpoints are responder rates. Across the clinical/tissue endpoints, 50 mg provides little or no consistent advantage over 25 mg.

Pooled ABTECT-1/2 Phase 3, week 8 — FCP reduction versus endoscopic and histologic endpoint response rates
Sources: Siegmund et al., ECCO 2026 DOP057 (FCP); Magro et al., ECCO 2026 P0922 and DDW 2026 (endoscopic/histologic endpoints)

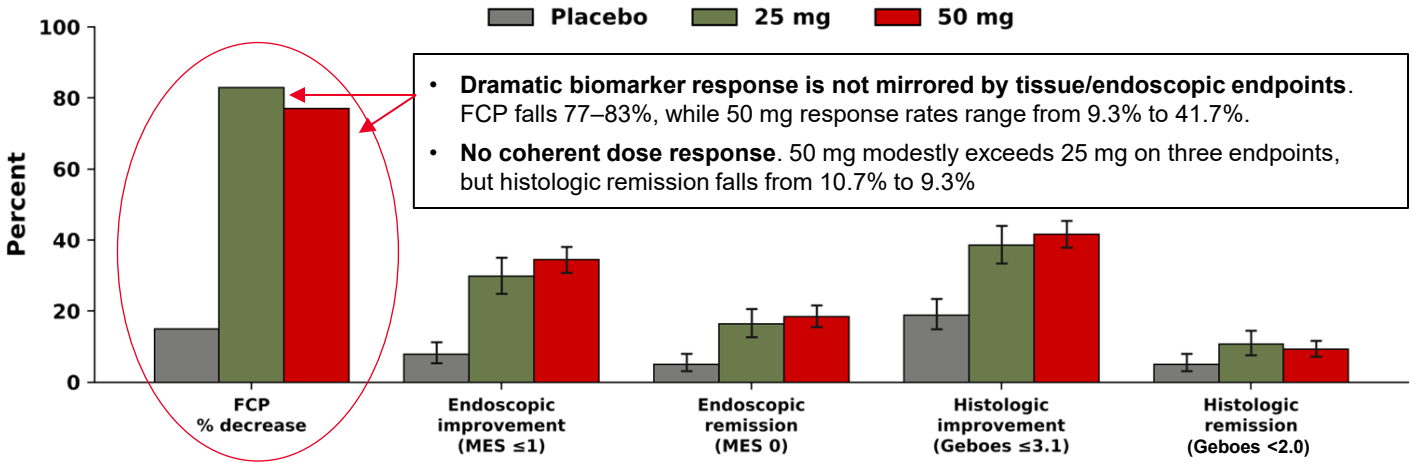


Chart methodology. Scorpion Capital reconstruction from sponsor-reported pooled ABTECT-1/2 data. FCP percent reductions are from Siegmund et al., ECCO 2026 DOP057; endoscopic and histologic response rates are from Magro et al., ECCO 2026 P0922 / DDW 2026. Error bars for binary endpoints are Scorpion-calculated 95% Wilson CIs from reported N; no dispersion was reported for FCP.

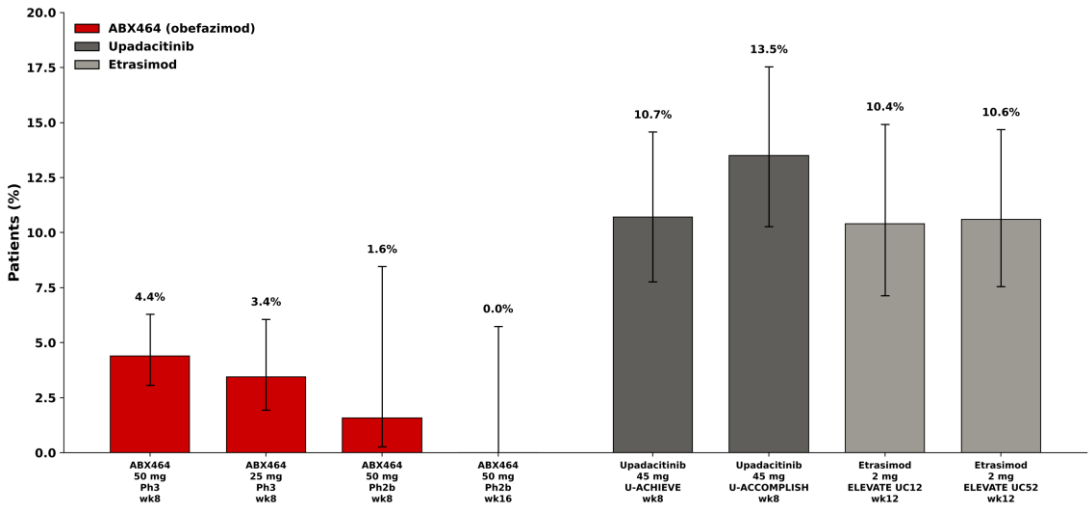
Sponsor-reported pooled ABTECT-1/2 week-8 results used in the reconstruction

Endpoint	Placebo % (N=317)	25 mg % (N=319)	50 mg % (N=636)
FCP, % decrease vs baseline	15	83	77
Endoscopic improvement (MES ≤1)	7.9	29.8	34.4
Endoscopic remission (MES 0)	5.0	16.3	18.4
Histologic improvement (Geboes ≤3.1)	18.9	38.5	41.7
Histologic remission (Geboes <2.0)	5.0	10.7	9.3

Sources: Siegmund et al., DOP057, ECCO 2026; Magro et al., DDW 2026; Magro et al., ECCO 2026 (P0922); Scorpion Capital analysis, modeling, estimates, and literature/publication review

On the same strict histo-endoscopic remission (HEMR) definition, ABX464 is the weakest of the compared UC regimens — 4.4% at 50 mg versus ~10–14% for upadacitinib and etrasimod. Its Phase 3 HEMR rate was low, and Phase 2b was weaker still.

Same strict HEMR definition across UC induction trials — endoscopic score 0 + Geboes <2.0



- **Same stringent endpoint across all comparisons.** HEMR requires both endoscopic normalization (MES 0) and histologic remission (Geboes <2.0).
- **ABX464 is lowest in Phase 3.** At 50 mg, HEMR is 4.4% versus 10.7–13.5% for upadacitinib and 10.4–10.6% for etrasimod — roughly one-third to two-fifths of the comparator rates..
- **Phase 2b was weaker still.** HEMR was 0–1.6% at week 8 across ABX464 doses; by week 16, only one patient in the 100 mg arm achieved HEMR

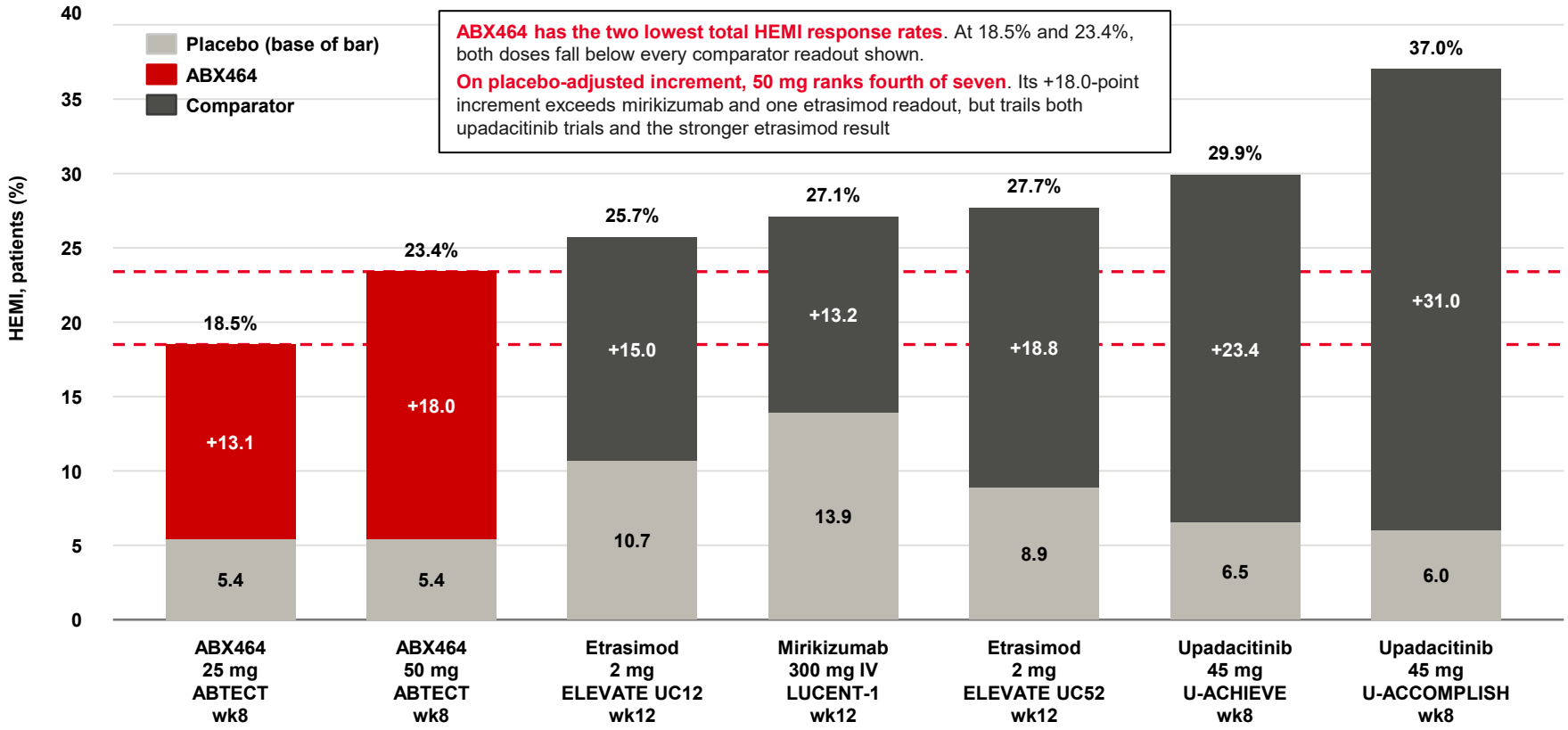
Arm	Phase 2b HEMR week 8	Phase 3 HEMR, week 8	Phase 2b HEMR, week 16
Placebo	2/64 (3.1%)	2/317 (0.6%)	0/64 (0.0%)
ABX464 25 mg	0/61 (0.0%)	11/319 (3.4%)	0/61 (0.0%)
ABX464 50 mg	1/63 (1.6%)	28/636 (4.4%)	0/63 (0.0%)
ABX464 100 mg	0/64 (0.0%)	NA	1/64 (1.6%)

Methods: All bars use the same strict composite endpoint: Mayo endoscopic score 0 plus Geboes histologic score <2.0. Bars show reported treatment-arm response rates; comparisons are cross-trial and not placebo-adjusted. ABX464 and upadacitinib are week 8; etrasimod is week 12. Error bars are Scorpion-calculated 95% Wilson CIs from reported n/N. Sources: Magro et al. 2026; Vermeire et al. 2022; upadacitinib U-ACHIEVE/U-ACCOMPLISH Phase 3; FDA etrasimod review.

Sources: Magro et al., DDW 2026; Vermeire et al. 2022; ClinicalTrials.gov NCT04023396; Upadacitinib UC Phase 3 program, ECCO 2022 P522; Magro et al., Clin Gastroenterol Hepatol 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABX464 also ranks at the bottom on histo-endoscopic improvement (HEMI) — both doses have the lowest total response rates among seven readouts using the same HEMI definition.

Histo-endoscopic improvement (HEMI) across UC induction trials using the same endpoint definition



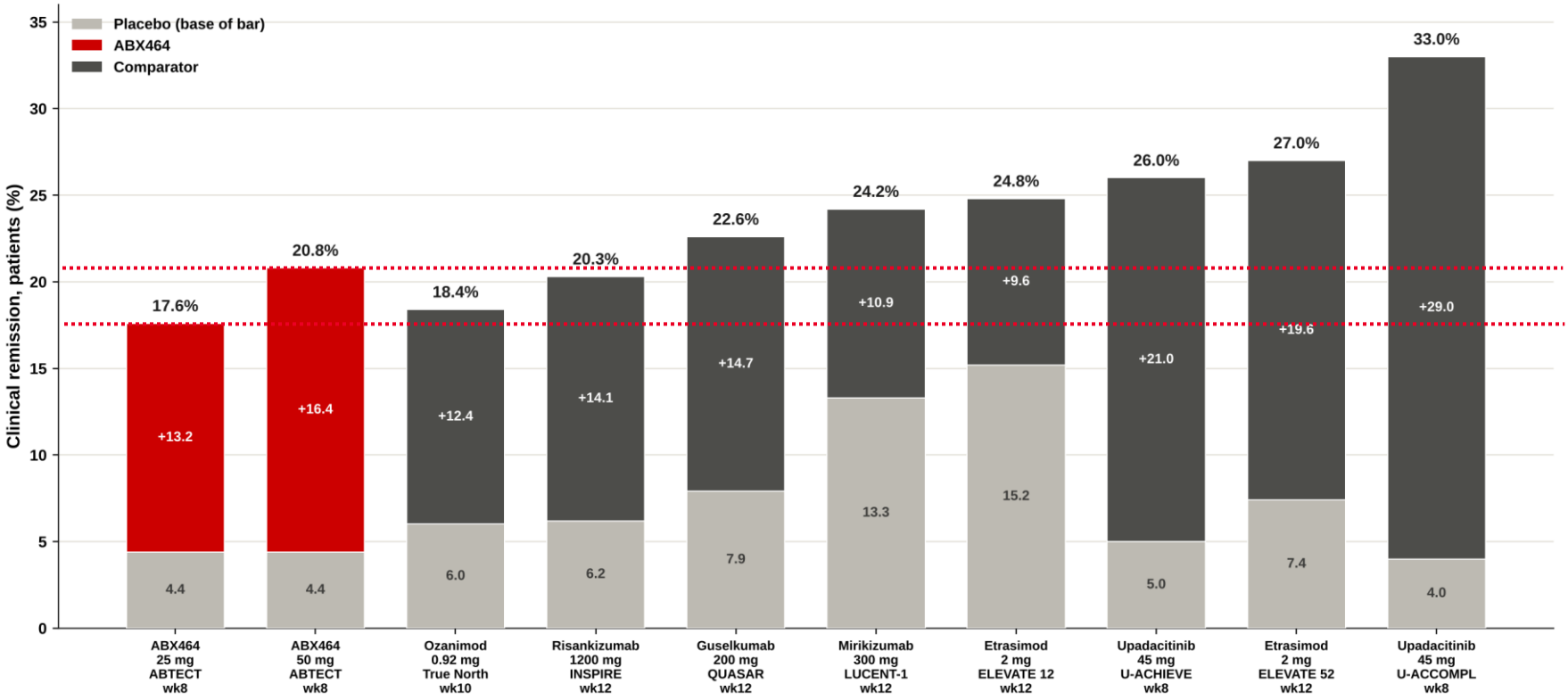
Methods: HEMI was defined consistently across the displayed trials as Mayo endoscopic score 0 or 1, with friability excluded, plus Geboes ≤3.1. Bars show each trial's published treatment and placebo rates; the grey base is placebo and the upper segment is the treatment-minus-placebo increment calculated by Scorpion Capital. Comparisons are cross-trial and not randomized head-to-head. Induction timepoints range from week 8 to week 12. No qualifying HEMI trial shown here was excluded.

Scorpion Capital reconstruction from published trial results. Drug and placebo response rates are source-reported; placebo-adjusted increments are calculated as treatment rate minus placebo rate

Sources: Magro et al. 2026; Danese et al. 2022; D'Haens et al. 2023; Sandborn et al. 2023; Magro et al. 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

ABX464's Phase 3 primary endpoint is unremarkable versus approved UC therapies — 20.8% clinical remission at 50 mg sits in the low-to-middle range across eight comparator readouts from six therapies.

Induction clinical remission across UC trials — treatment response with placebo base and treatment increment



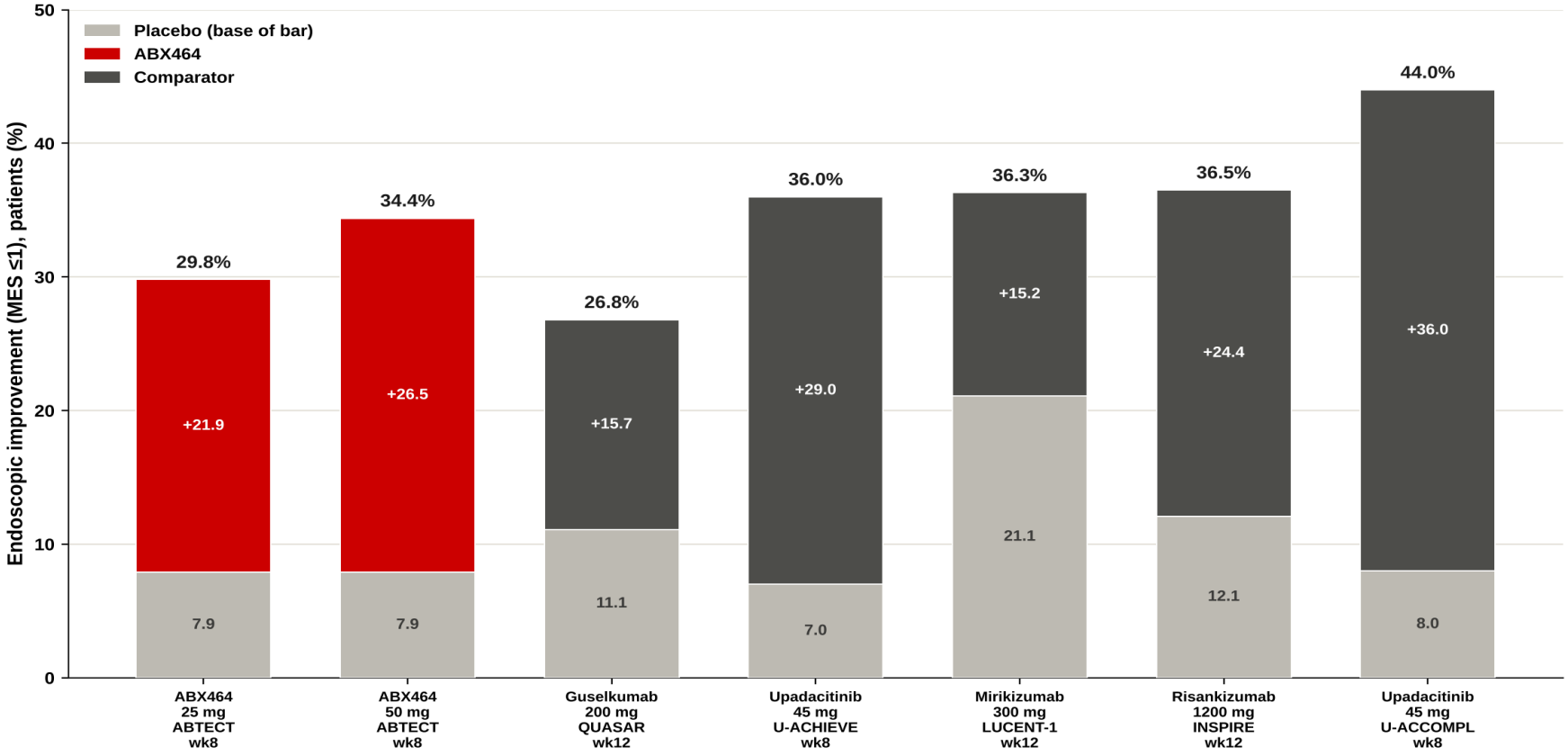
Methods: Clinical remission was defined consistently as stool-frequency subscore 0 or 1, rectal-bleeding subscore 0, and Mayo endoscopic subscore 0 or 1 with friability excluded. Bars use published treatment and placebo rates; grey is placebo and the upper segment is the treatment-minus-placebo increment calculated by Scorpion Capital. Cross-trial comparison; induction timepoints range from week 8 to week 12.

Scorpion Capital reconstruction from published trial results; all underlying treatment and placebo response rates are source-reported

Sources: Sands et al. 2025; Sandborn et al. 2021; Louis et al. 2024; Rubin et al. 2025; D'Haens et al. 2023; Sandborn et al. 2023; Danese et al. 2022; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Endoscopic improvement is similarly undifferentiated — ABX464 50 mg reaches 34.4%, around the middle of the comparator set.

Induction endoscopic improvement across UC trials — placebo base + treatment increment



Methods: Endoscopic improvement is Mayo endoscopic subscore ≤1. Bars use published treatment and placebo rates; grey is placebo and the upper segment is the treatment-minus-placebo increment calculated by Scorpion Capital. Cross-trial comparison; induction timepoints range from week 8 to week 12.

Scorpion Capital reconstruction from published trial results; underlying treatment and placebo response rates are source-reported.

Sources: Magro et al. 2026; Danese et al. 2022; D'Haens et al. 2023; Louis et al. 2024; Allegretti et al. 2025; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Phase 2b showed the same lack of dose response seen in Phase 3: across a fourfold dose range, 25, 50 and 100 mg all improved pMMS by ~1.8 points at week 4, after which the drug–placebo separation largely stopped growing.

Phase 2b pMMS trajectory — published data and Scorpion reconstructions of the placebo-adjusted effect

A. Published pMMS change from baseline by visit

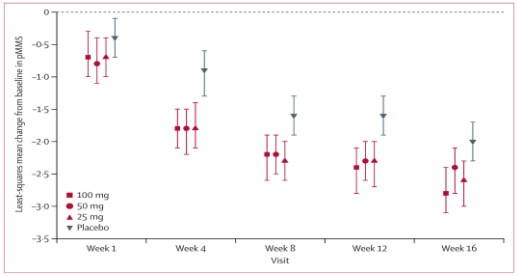


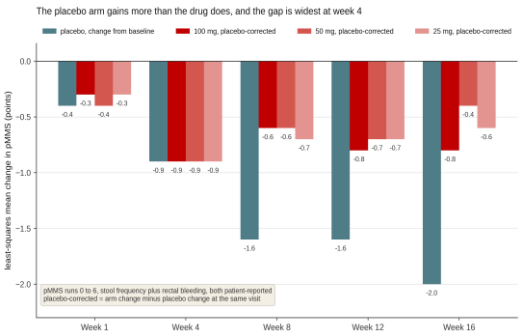
Figure 2: **Mean change from baseline in pMMS in full analysis set**
Vertical bars show 95% CIs. pMMS is the sum of assessment scores (0–3) of stool frequency and rectal bleeding. pMMS=partial modified Mayo Score.

All three doses converge. At week 4, pMMS improves by ~1.8 points at 25, 50 and 100 mg versus ~0.9 for placebo — essentially identical responses across a fourfold dose range.

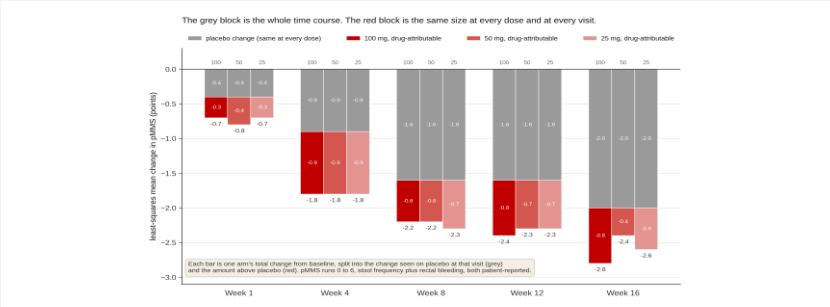
The incremental treatment effect then largely plateaus. From week 4 onward, the active arms continue to improve, but placebo improves substantially as well; the treatment–placebo gap changes relatively little.

The pattern persists through week 16. Much of the additional improvement occurs alongside continued placebo improvement rather than increasing dose-dependent separation; no consistent dose gradient emerges

B. Placebo-adjusted pMMS change by visit



C. Arithmetic decomposition: placebo change + treatment–placebo difference



Methods: pMMS is the sum of stool-frequency and rectal-bleeding subscores; lower scores indicate improvement. Panel A reproduces Vermeire et al. Figure 2; Panels B and C are Scorpion Capital reconstructions from digitized plotted values. Panel B subtracts placebo change from each active arm at each visit; Panel C algebraically separates each treatment-arm change into placebo change plus the treatment–placebo difference. The decomposition is descriptive, not causal.

Sources: Vermeire et al. 2022, Phase 2b induction, Lancet Gastroenterol Hepatol. 2022;7:1024–1035, Figure 2. Panels B/C: Scorpion Capital reconstruction from digitized Figure 2 values.

Histology endpoint shopping: Phase 2b prospectively included three histology indices -- Robarts, Geboes and Nancy -- with Robarts specifically designated to confirm mucosal healing, but only one survived into Phase 3. Robarts -- the most reproducible -- failed the prespecified 50 mg statistical gate and was removed; Nancy was collected but not reported; Geboes "worked" and became the sole histology framework carried forward. The sequence suggests cherry-picking a histology measure vs. independent confirmation across them.

The source documents show three separate histology frameworks prospectively included in the program

ABX464-103 Statistical Analysis Plan (10 May 2021)

Secondary objectives included rectal/sigmoidal infiltrates assessed with all three histology scales at Weeks 8 and 16. The SAP also specifies change from baseline in all three scores.

15.2.1.11. Reduction relative to baseline of infiltrate/histopathology (rectal biopsies) using the Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales at Week 8 and Week 16

Change from baseline in RHI, Geboes and Nancy scores will be determined at Week 8 and Week 16. The number of patients with a reduction relative to baseline in RHI, Geboes and Nancy scores will also be recorded. Reduction relative to baseline is defined in Section 6.6.

ABX464-104 Maintenance Protocol (11 Jul 2022)

The maintenance protocol describes RHI as reproducible, responsive and valid. Geboes and Nancy were also read "for completeness purposes."

ABIVAX Clinical Study Protocol Study code: ABX464-104

for assessment according to Robarts Histopathology Index (RHI), the Geboes and Nancy Histology Scoring Scales (please refer to the lab manual) and for miRNA-124 determination (RNA later).

RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is based on the evaluation of four main parameters: chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in the epithelium and erosion/ulceration. Overall, this histological index has been reported to be reproducible, responsive and valid and will be used for confirmation of the mucosal healing. The patient's biopsies will be also read according to the Geboes and Nancy Histology Scoring Scales for completeness purposes.

Phase 2b did not start with a single histology measure -- three indices were prospectively specified, and Robarts was expressly positioned as the confirmatory mucosal-healing index.

Sources: Vermeire et al. 2022 ; ABX464-103 SAP page 54, https://cdn.clinicaltrials.gov/large-docs/03/NCT03760003/SAP_001.pdf; ; ABX464-104 protocol page 33, https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Robarts Histopathology Index (RHI) and Nancy Index (NI) are generally viewed as better validated for randomized UC trials, while Geboes is older and widely used but less attractive – thus, ECCO's 2020 histopathology position paper specifically recommends RHI or NI for randomized controlled trials. Robarts has substantially higher published inter-rater reliability.

Robarts was specifically developed from Geboes components to create a more reliable trial instrument. International consensus found RHI and Nancy appropriate for assessing disease activity. Experts were less comfortable with Geboes.

Published literature comparing histology endpoints for UC trials

ECCO Position Paper: Harmonization of the Approach to Ulcerative Colitis Histopathology

erosion and ulceration as a minimum requirement for the definition of histological remission. For randomized control trials we recommend the use of the Robarts histopathology index [RHI] or the Nancy index [NI]. For observational studies or in clinical practice we recommend the use of the NI. To predict the risk of future neoplasia in UC, cumulative histological scores over time are more useful than single scores.

An international consensus to standardize integration of histopathology in ulcerative colitis clinical trials

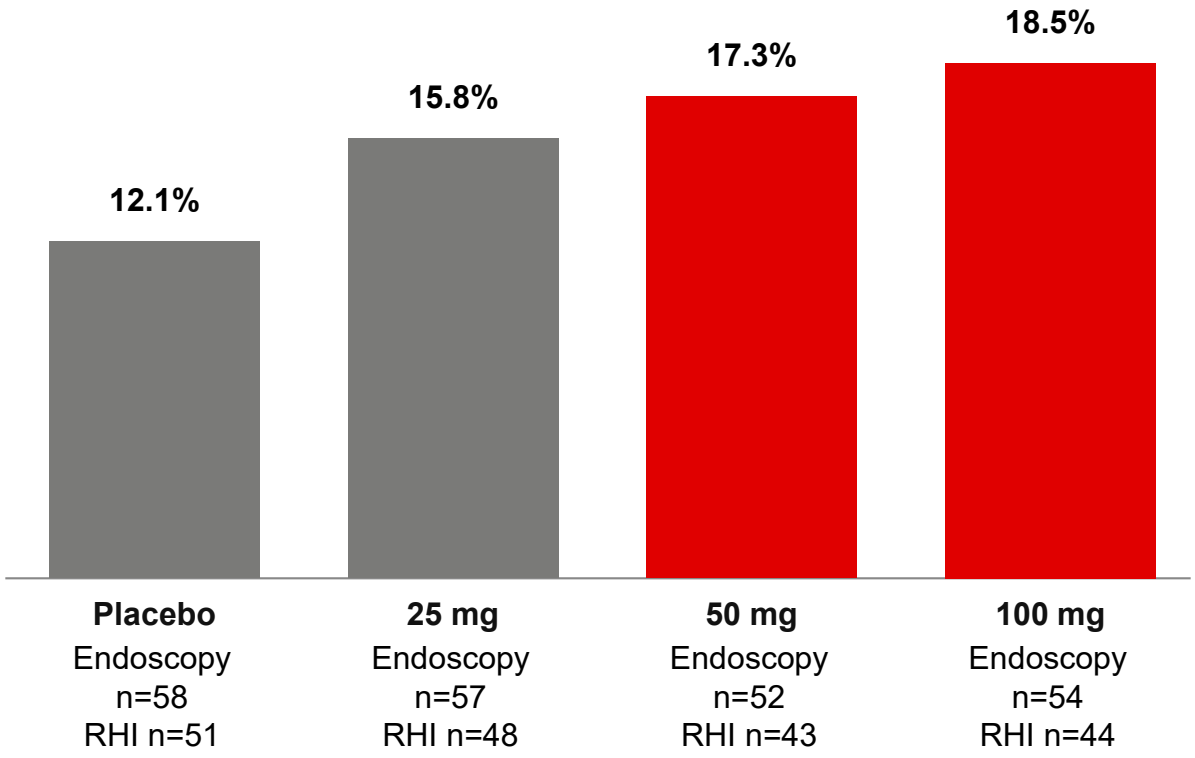
Several histology indices were considered. The Geboes Score was considered appropriate for assessing histologic activity in UC and classifying active disease, although the panel acknowledged that it was not specifically designed for measuring change in histologic activity due to the hierarchical scoring. Similarly, panelists were uncertain if converting the Geboes Score to a continuous 0 to 22 scale was appropriate for this purpose. The panelists

Sources: https://pubmed.ncbi.nlm.nih.gov/32504534/; https://pmc.ncbi.nlm.nih.gov/articles/PMC8851891/; Scorpion Capital analysis, modeling, estimates, and literature/publication review

The published Robarts dataset was incomplete even among patients with endoscopy — 12–19% are missing from the reported RHI analysis at week 8, per the Vermiere (2022) supplemental data table. The unexplained gap in the published Robarts dataset is a clear data-completeness red flag.

Week 8: endoscopy data available, but no corresponding patient included in the published Robarts analysis

Percent of endoscopy patients per arm not represented in the published Robarts analysis



What this establishes

- The published supplement reports endoscopy n and RHI n side-by-side for the same week-8 analysis set.
- The missing share ranges from 12.1% to 18.5% across arms.
- The publication does not explain why those patients are absent from the RHI analysis..

Scorpion calculation: (endoscopy n − RHI n) / endoscopy n. Week-8 values verified against Vermeire et al. 2022 Supplementary Table 3 (per-protocol analysis set).

Sources: Vermeire et al., Lancet Gastroenterol Hepatol. 2022;7:1024–1035, Supplementary Table 3. Percentages are Scorpion Capital calculations from source-reported n; Scorpion Capital analysis, modeling, estimates, and literature/publication review..

The 50 mg Robarts analysis then failed ABVX's first prespecified statistical gate -- p=0.187 per protocol and p=0.200 in the full analysis set -- non-significant vs. placebo.

ABX464-103 SAP §7.4: the closed testing sequence starts at 50 mg and advances only if the prior comparison is significant

Prespecified closed sequence -- ABX464-103 Statistical Analysis Plan (10 May 2021), excerpt

No adjustment for multiple comparisons is needed, as closed procedures will be applied in testing each dose level vs placebo. The dose testing will commence with comparing the ABX464 50mg dose with placebo. If this is significant at a 5% two-sided level (i.e. p<0.05) a comparison against placebo will be carried out at the ABX464 100mg dose. Again, if significance at a 5% level for this test is observed the procedure will be repeated at the ABX464 25mg dose. If in this sequence of comparisons of ABX464 dose levels to placebo, one is not significant (i.e., p >= 0.05) the additional comparisons to placebo will not be performed. Should any of the comparisons against placebo be significant, the different dose groups will also be compared, using the same significance level.

1st gate
50 mg vs placebo

→ only if p<0.05

2nd
100 mg vs placebo

→ only if p<0.05

3rd
25 mg vs placebo

STOP AT STEP 1: the 50 mg Robarts comparison is non-significant, so the prespecified sequence does not advance.

Robarts Histopathology Index — Week 8

Measure	25 mg	50 mg	100 mg
Difference vs placebo	−4.0	−2.6	−4.1
Per-protocol p	0.030	**0.187**	0.041
Full-analysis-set p	0.030	**0.200**	0.052

Sources: Vermeire et al. 2022 ; ABX464-103 SAP page 54, https://cdn.clinicaltrials.gov/large-docs/03/NCT03760003/SAP_001.pdf; ; ABX464-104 protocol page 33, https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf; Scorpion Capital analysis, modeling, estimates, and literature/publication review

After Phase 2b, three histology indices became one: Robarts and Nancy disappear from Phase 3, while every Phase 3 histology endpoint is Geboes-based. And even then, the surviving Geboes framework did not produce compelling tissue efficacy in Phase 3 — only 9.3% achieved histologic remission at 50 mg and HEMR was 4.4%.

The source documents show three separate histology frameworks prospectively included in the Phase2b -- dwindling to one in Phase 3

PHASE 2b

→

All Phase 3 histology efficacy definitions are Geboes-based:

ROBARTS (RHI)

- Designated to confirm mucosal healing
- 50 mg gate: p=0.187
- Absent from Phase 3 efficacy endpoints

NANCY

- Prespecified and collected
- No Nancy result located in the publication/ supplements reviewed
- Absent from Phase 3 protocol

GEBOES

- Produced reported positive histology readouts
- Carried forward into Phase 3

GEBOES

Histologic improvement

Histologic remission

HEMI

HEMR

ABTECT-1 Protocol V5.1 defines each using Geboes scoring.

Sources: Vermeire et al. 2022 ; ABX464-103 SAP page 54, https://cdn.clinicaltrials.gov/large-docs/03/NCT03760003/SAP_001.pdf; ; ABX464-104 protocol page 33, https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf; Scorpion Capital analysis, modeling, estimates, and literature/publication review

Chapter 23. ABVX's flimsy U.S./North American Phase 3 subgroup data risks intense FDA scrutiny

North American ABTECT subgroup data suggests high FDA risk/scrutiny of geographic imbalances – and leads us to question if Phase 3 was driven by artificially-inflated efficacy in low-quality countries. ABVX has not published country-level enrollment nor placebo-adjusted deltas and adverse events, but an ECCO Feb 2026 poster provided NA data – we start here.

ECCO Feb 2026 poster – ABTECT North American subgroup data

P0694 Pooled analysis of efficacy and safety of once-daily oral obefazimod in North American patients from the ABTECT Phase 3, double-blind, placebo-controlled induction trials FREE

Results: Among the 1272 pts randomized in the ABTECT trials, 122 were NA pts (116 pts from USA and 6 pts from Canada). Baseline demographics and disease characteristics were well balanced between treatment groups and generally comparable between NA pts and the overall study population. In the pooled analysis, a higher proportion of NA pts receiving Obe-25 or Obe-50 vs. PBO achieved clinical remission (Obe-25-PBO difference: 13.6%, p=0.0218; Obe-50-PBO difference: 13.2%, p=0.0235), clinical response, and symptomatic remission with nominal significance (Table). Headache was the most common TEAE (Obe-25: 29.2%; Obe-50: 24.2%; PBO: 5.6%). Among NA pts, no serious TEAEs occurred with Obe-25, and the rate with Obe-50 was similar to PBO (3.2% vs 8.3%, respectively). TEAE leading to study discontinuations were less frequent with Obe-25 (4.2%) and Obe-50 (6.5%) vs PBO (13.9%). No opportunistic infections or malignancies were reported.

Conclusion: In the ABTECT induction trials, clinically meaningful improvements in efficacy measures were observed, and Obe treatment demonstrated a favorable safety profile in NA pts, consistent with the overall study population.

Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078

The ECCO poster indicates 122 NA patients, 10% of ABTECT total. NA placebo-adjusted remission rates were 13.6% 25mg and 13.2% 50mg, in-line with the global study population – favorable subgroup data, at first glance...although only 3 and 8 active-treated patients achieved remission in the 25mg and 50mg arms, respectively.

ECCO Feb 2026 poster – ABTECT North American subgroup data, study table

Table: 8-week efficacy of obefazimod in North American vs global population - pooled ABTECT trials

		North American pts* (N=122)			Global population (N=1272)		
		PBO (N= 36)	Obe 25 (N= 24)	Obe 50 (N=62)	PBO (N= 317)	Obe 25 (N= 319)	Obe 50 (N=636)
Clinical remission	% (n)	0	12.5 (3)	12.9 (8)	4.4 (14)	17.6 (56)	20.8 (132)
	Placebo adjusted Δ %		13.6	13.2		13.2	16.4
	p-value		p=0.0218	p=0.0235		p<0.0001	p<0.0001
Clinical response	% (n)	16.7 (6)	54.2 (13)	41.9 (26)	30.9 (98)	59.6 (190)	62.1 (395)
	Placebo adjusted Δ %		37.8	25.5		28.6	31.2
	p-value		p=0.0017	p=0.0143		p<0.0001	p<0.0001
Endoscopic improvement	% (n)	5.6 (2)	16.7 (4)	21.0 (13)	7.9 (25)	29.8 (95)	34.4 (219)
	Placebo adjusted Δ %		11.1	12.7		21.9	26.6
	p-value		p=0.1495	p=0.0844		p<0.0001	p<0.0001
Symptomatic remission	% (n)	2.8 (1)	25.0 (6)	29.0 (18)	19.9 (63)	37.9 (121)	40.7 (259)
	Placebo adjusted Δ %		23.5	26.3		18.1	21.0
	p-value		p=0.0030	p=0.0022		p<0.0001	p<0.0001
HEMI	% (n)	2.8 (1)	4.2 (1)	16.1 (10)	5.4 (17)	18.5 (59)	23.4 (149)
	Placebo adjusted Δ %		2.5	11.3		13.2	18.2
	p-value		p=0.5930	p=0.0889		p<0.0001	p<0.0001

Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078

However, the North America placebo-adjusted remission only looks in-line with the global cohort because of curiously low placebo remission – 0/36 patients – rendering "North America replicated global efficacy" a fiction. Another red flag: the subgroup data is post-hoc + pooled. combining ABTECT-1 + ABTECT-2 vs. showing North America results separately.

ECCO Feb 2026 poster – ABTECT North American subgroup data, study table

Table: 8-week efficacy of obefazimod in North American vs global population - pooled ABTECT trials

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Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078

North America statistical significance is incredibly fragile – if just one of 36 pbo patients had remitted, 50mg arm p-value rises from 0.025 to a farcical 0.148 and statistical significance vanishes. P=0.32 with two placebo remitters – a debacle. The 25mg result is even flimsier. Even with zero pbo remitters, p=0.06 -- nonsignificant under two-sided Fisher's exact test. The abstract's reported p=0.0218 and 0.0235 fails to disclose the test used. If one or two remitters for 25mg, p rises to 0.29 or 0.38 – weaker than 50mg.

ECCO Feb 2026 poster – ABTECT North American subgroup "efficacy" is fragile

One placebo remitter eliminates the 50-mg arm's significance under two-sided Fisher's exact test; the 25-mg arm is already nonsignificant even with zero placebo remitters.

25 mg

Using unadjusted two-sided Fisher's exact test:

- **0/36 placebo vs 3/24 25mg: p ≈ 0.059**
- **If just 1 of the 36 placebo patients had remitted: 1/36 vs 3/24 → p ≈ 0.292**
- 2 placebo remitters → **p ≈ 0.380**

50 mg

Using unadjusted two-sided Fisher's exact test:

- **0/36 placebo vs 8/62 50mg: p ≈ 0.025**
- **If just 1 of the 36 placebo patients had remitted: 1/36 vs 8/62 → p ≈ 0.148**
- 2 placebo remitters → **p ≈ 0.317**

Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078' Scorpton Capital analysis and estimates

The global pbo remission rate was 4.4% - already unusually low and less than half the 9-12% found in reviews of UC trials, thus reeking of a gamed study. But even using ABVX's 4.4% rate to 36 NA pbo patients, the expected number of remitters is ~1.6 – meaning the expected outcome under the trial's own global pbo behavior is in the p≈0.15 to 0.38 range. Thus, the entire purported NA significance rests on the zero pbo remitters anomaly.

ECCO Feb 2026 poster – ABTECT North American subgroup data, global remission rate 4.4%

Table: 8-week efficacy of obefazimod in North American vs global population - pooled ABTECT trials

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	p-value		p=0.5930	p=0.0889		p<0.0001	p<0.0001

Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078' Scorpton Capital analysis and estimates; published reviews indicating 9-12% pbo remission rates in UC trials -- https://pubmed.ncbi.nlm.nih.gov/41206929/; https://pubmed.ncbi.nlm.nih.gov/28886205/

Another red flag suggests NA efficacy is an artifact of an artificial 0/36 placebo remission rate. The placebo arm wasn't inert, showing clinical response (17%), endoscopic improvement (6%), and symptomatic remission (3%) – yet none of that improvement converted to a single pbo composite remission endpoint, as one might expect. We are curious which modified-Mayo component killed remission classification, thus driving stat sig.

ECCO Feb 2026 poster – ABTECT North American subgroup data

Table: 8-week efficacy of obefazimod in North American vs global population - pooled ABTECT trials

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Source: https://academic.oup.com/ecco-jcc/article/20/Supplement_1/jjaf231.875/8433078

We note other concerning oddities in NA, with the objective endpoint – endoscopic improvement -- failing badly. P=0.15 and 0.08 in 25mg and 50mg respectively -- half the global delta vs. pbo. The only endpoints that hit are patient-reported, a pattern that typically merits FDA scrutiny: weak objective endpoint + "robust" subjective endpoint in the highest-integrity geography, ignoring the dubious quality of ABTECT North American sites to begin with.

ECCO Feb 2026 poster – ABTECT North American subgroup data

Table: 8-week efficacy of obefazimod in North American vs global population - pooled ABTECT trials

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