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Catalytic phototoxicity may explain the dose-related skin cancers in Abivax's phase 3 trials.

Scorpion Capital commissioned a fluorescence absorption assay that demonstrated ABX464 absorbs UVA light in the most dangerous wave band, deep within the stem cell layer where squamous and basal cell cancers are formed.

Abstract

Rationale

We characterized the physicochemical and photophysical behavior of ABX464 and found properties that may bear directly on the dose-related skin cancers observed in Abivax's Phase 3 trials. By fluorescence spectroscopy we found that ABX464 is a charge-transfer fluorophore absorbing UVA at 349 nm with a resolved vibronic band near 360 nm across a shallow trough between them. Both maxima exceeded the ICH S10 photoreactivity threshold more than 7.5-fold. Absorption stayed above that threshold across 95% of the sun's UVA, including the long wavelengths that penetrate deep into skin. Excitation carried energy sufficient for both type I and type II photochemistries that create reactive oxygen species (ROS). ABX464, as a highly lipophilic compound with logP ~6, is predicted to partition into cell, organelle and nuclear membranes adjacent to chromatin. Basal keratinocytes express LDL receptors, which are expected to deliver ABX464 parent to the most active skin cells, especially any precancerous lesions. The basal keratinocytes and melanocytes of the germinative layer are the dividing stem cells that give rise to melanoma and non-melanoma skin cancer and the population most vulnerable to mutagens. A photosensitizer of this class may propagate lipid peroxidation chains hundreds of lipids long; each oxidized lipid in that chain can damage DNA while the drug returns to ground state to be excited again. In the eye these actions may produce cataracts and keratopathy, which may be why Abivax instructs patients to wear sunglasses.

Quinine, a quinoline like ABX464, is the reference standard for fluorescence quantum-yield measurements (Brouwer 2011) and a known photosensitizer. Quinine hydrochloride is the positive control for the OECD Test Guideline 495 reactive oxygen species (ROS) assay (OECD 2019). ABX464 is built on the same quinoline chromophore. In the adverse event section of the Abivax clinical protocol[1] (version 5.1, 11 July 2022, page 39, section 8.2 "Definition of an AESI", under the heading "Skin Lesions (regardless of its severity)", "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." Abivax only disclosed the phototoxicity of the N-Glucuronide metabolite with no mention of the parent molecule in the Clinical protocol, as far as we could locate. We reasoned that if the glucuronidated metabolite was phototoxic, ABX464 would be equally or more phototoxic since, chemically, the N-Glucuronide substituent would not be expected to significantly affect the photophore. Since Abivax has disclosed no details that we could find beyond a positive in vivo

[1] Phase 2b clinical study protocol, https://cdn.clinicaltrials.gov/large-docs/96/NCT04023396/Prot_000.pdf

toxicity study for the N-Glucuronide, we contracted an independent laboratory to measure its absorption spectrum for the parent ABX464.

We demonstrated that ABX464 is a charge-transfer fluorophore (Scorpion Capital DLS Autofluorescence, 2026) with intrinsic fluorescence, a property that would allow it to repeatedly cycle through excitation and relaxation phases in sun-exposed skin at energies that may damage DNA and the enzymes that repair it. Abivax, to the best of our knowledge, has not disclosed the absorption spectrum for either the N-glucuronide metabolite or the parent molecule, critical information that informs skin penetration and how much energy per mole the UV excitation captures per photon (ε). For the absorption component that we tested, ABX464 possesses a particularly high-risk profile as its absorption spectrum was a wide band the center of the sunlight UVA band, peaking within the most deeply penetrating spectrum and an extinction coefficient roughly 8-times over the FDA gating limit.

Materials and methods

Instrument

Shimadzu RF-6000 spectrofluorometer (S/N: A40245701603SA), LabSolutions RF software v1.15. Excitation wavelength: 350 nm. Emission scan: 400–650 nm or 200–650 nm. Data interval: 1.0 nm. Scan speed: 2000 nm/min. EX/EM bandwidth: 5.0 nm / 5.0 nm. Sensitivity: Auto.

Absorbance spectrum

We recorded the absorbance spectrum in acetonitrile due to ABX464's limited aqueous solubility. For absorbance, ABX464 was dissolved in acetonitrile (HPLC grade, Sigma-Aldrich) at 0.057 mM (57 µM) and scanned from 200 to 700 nm on a PerkinElmer LAMBDA 365 UV/Vis spectrophotometer, 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 from the peak absorbances was calculated by the Beer-Lambert relation, $\varepsilon = A/(cl)$.

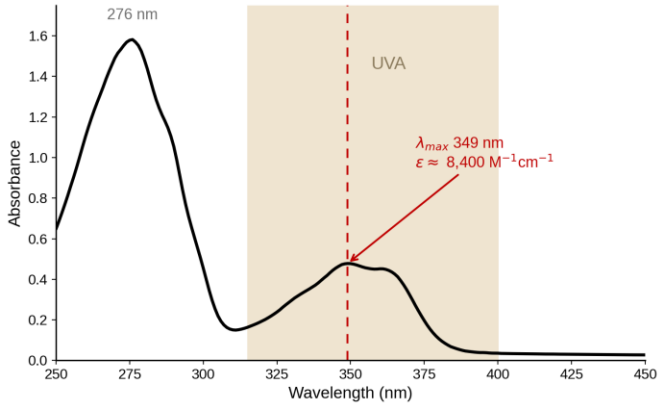
Results

ABX464 absorbs strongly across most of the UVA window

As shown in Figure 1, we observed 3 absorption maxima for ABX464. Two in the two long-wavelength region, at 349 nm (ε 8,400 $M^{-1}cm^{-1}$) and 360 nm (ε 7,900 $M^{-1}cm^{-1}$) and another at 276 nm. The UVA bands together span most of the deeply skin-penetrating ultraviolet A band known to reach the dermal stem cells. Thus, ABX464 absorbs over most of the UVA band within the most dangerous region for skin cancer initiation and progression of cancer. The energy maximum for ABX464 was roughly 8-fold above the ICH S10 photoreactivity safety threshold of 1,000 $M^{-1}cm^{-1}$ (315 to 400 nm) (ICH, 2013). The third absorption peak was at 276 nm (ε 27,800 $M^{-1}cm^{-1}$), and of lesser concern for photosensitivity (Diffey, 1991; D'Orazio et al., 2013).

The dual maximal UVA peaks were about 876 cm^{-1} apart as shown in Figure 1. This is a known signature of a vibrational electron transfer pattern (Lakowicz, 2006; Turro et al., 2010). Vibronic structure of this kind arise from rigid, planar chromophores whose excited-state geometry is not changed during excitation, a finding consistent with ABX464's planar aromatic geometry (Turro et al., 2010). The two maxima were separated by a shallow trough with the second nearly as intense as the first so that the molecule absorbs highly throughout 95% of the dangerous UV bands, 345 to 362 nm with significant absorption out to 380 nm.

Figure 1. Molar extinction of ABX464 across the long UVA window (shaded), at energies sufficient to produce Type 1 and Type 2 reactive oxygen species (ROS).



Absorbance spectrum of ABX464 (57 µM in acetonitrile), scanned from 200 to 700 nm on a PerkinElmer LAMBDA 365 UV/Vis spectrophotometer in a 1 cm quartz cuvette at 25 °C against a matched acetonitrile blank. Within the ultraviolet A band (315 to 400 nm, shaded) absorption reaches a maximum at 349 nm (ε 8,400 $M^{-1}cm^{-1}$) with a resolved secondary maximum near 360 nm (ε 7,900 $M^{-1}cm^{-1}$). Scorpion Capital, original experiment, 2026.

ABX464 excites and absorbs where sunlight penetrates skin deeply. Photon penetration increases with increasing wavelength and can produce energy sufficient to catalyze reactive oxygen species in neighboring proteins, lipids and DNA in dividing keratinocytes. At this energy level ABX464 is predicted to have the potential to drive both Type 1 (hydrogen extraction) and Type 2 (singlet oxygen peroxidation) reactions generating reactive oxygen species (ROS). ROS damage DNA and may also damage the repair enzymes. Phototoxicity is renewable such that each molecule may excite and use that energy to damage cellular components repeatedly as it decays back to a resting state. We estimate that a single ABX464 molecule can be excited and re-excited every 60 seconds in keratinocytes, each excitation providing a new opportunity for cellular damage.[2]

[2] *Excitation rate calculated as $R = \sigma\Phi$, where σ is the absorption cross-section and Φ the photon flux. $\sigma = 3.82 \times 10^{-21} \times \varepsilon = 3.1 \times 10^{-17}$ cm^2 using the mean measured ε of approximately 8,000 $M^{-1}cm^{-1}$ across 349 to 365 nm. $\Phi = 1.6 \times 10^{15}$ photons $cm^{-2}s^{-1}$, from the 8.64 Watts/$meter^2$ of solar irradiance in that band (ASTM G173-03, AM1.5, Figure 2) divided by the photon energy at the 357 nm band centre (5.56×10^{-19} J). This gives 0.048 excitations per molecule per second, or one every 21 seconds, at the skin surface under clear-sky noon sun. Attenuation through the epidermis reduces the rate at depth roughly in proportion to UVA transmission, giving one excitation every 50 to 70 seconds in the proliferative keratinocyte compartment at 40 to 50 µm, where transmission at 360 nm is 37 to 30 percent. At 80 µm, where transmission is 14 percent, the interval is 150 seconds, and that is the figure used for the photon capture column of Table 9. The attenuation curve is anchored on the published 14 percent transmission at 360 nm at 80 µm. The molecule returns to the ground state after each cycle and is not consumed so a single drug molecule will repeatedly excite. We have provided the rate of excitation, not of reactive oxygen production (box 1, experiment 3); we found no disclosure of the latter.*

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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.

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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.