Evaluate Vantage

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Aldeyra needs more Tranquility

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A pivotal failure sees the group tinker with a second phase 3 trial, and the delay looks like good news for Bausch.

Getting a result in dry eye disease studies can be hard, as Aldeyra has just found out. The pivotal Tranquility trial of the group's lead project, reproxalap, failed to hit its primary endpoint of ocular redness, a sign of disease.

Aldeyra reckons all is not lost, and is tinkering with its other phase 3 signs study, Tranquility-2, in the hope of getting the data it needs for filing. Even if reproxalap is eventually approved, competition in dry eye is growing, with Oyster Point's Tyrvaya recently getting the go ahead and a new contender looming in the shape of Bausch Health Companies' NOV03.

Signs and symptoms

For approval in dry eye the FDA requires a project to show a benefit on both the signs and symptoms of the disorder in at least two clinical trials apiece.

On symptoms, Aldeyra plans to submit data from part one of the phase 3 Renew trial, as well as a phase 2 Formulation study, which found a benefit on ocular dryness. On signs, Aldeyra will use data from a recently completed phase 2 study, which showed an improvement in ocular redness with reproxalap versus vehicle. The original plan had been to add the results of Tranquility to the package, but this has now been hastily redrawn.

While Tranquility missed the ocular redness endpoint, it did show a benefit on a secondary endpoint, the Schirmer test, which measures tear production. Aldeyra claimed statistical significance on the latter, but this can only be considered exploratory given the primary endpoint fail.

Still, this finding has given the group a path forward, it believes. Tranquility-2 also had ocular redness as its primary endpoint, but the study will now evaluate both this and the Schirmer test as co-primaries, and will be deemed a success if either of these hits.

Aldeyra has also enlarged Tranquility-2, from 300 to up to 400 patients. Results, which had been due by the end of the year, are now expected in mid-2022, which is also when the group plans to file for approval.

The FDA has yet to approve this arrangement, but the company pointed out that the Schirmer test had been used to support the approval of other dry eye products. Investors were not convinced, and Aldeyra opened down 45% this morning.

The company slipping in news of a delay to reproxalap in its second indication, allergic conjunctivitis, probably did not help. The FDA has asked Aldeyra to carry out another allergen chamber trial here.

Sellside consensus compiled by *Evaluate Pharma* puts 2026 sales of reproxalap at $312m in dry eye disease and $101m in allergic conjunctivitis.

Competition

Existing dry eye drugs, such Abbvie's Restasis and Novartis's Xiidra, leave a lot to be desired, so perhaps it is no wonder that plenty of other players are taking aim at this space.

The next to do so could be Bausch, whose NOV03 has shown improvements in both signs and symptoms in two pivotal trials, Gobi and Mojave (*Bausch boosted ahead of eye spin-off, April 14, 2021*).

Such emphatic results are far from the norm, however, and a look at the table below shows that Aldeyra is not the only one pressing on despite previous failures.

One company whose persistence paid off is Kala Pharmaceuticals, whose ocular corticosteroid Eysuvis got the FDA nod just over a year ago. Still, that product only sold $5.1m in the first nine months of this year, and Kala has seen its value melt away – its market cap is now just $90m.

Selected novel agents in phase 3 development for dry eye disease

Project	Company	Description	Trial details
NOV03	Bausch Health Companies/Novaliq	Lipid regulator	Gobi hit Apr 2021; Mojave hit Sep 2021; US filing planned H1 2022
RGN-259	Regentree (Regenerx Biopharmaceuticals/HLB Therapeutics joint venture)	Thymosin β-4 receptor agonist	Ph3 Arise-3 study failed in Mar 2021 but companies have FDA pre-BLA meeting Feb 28, 2022
Reproxalap ophthalmic solution	Aldeyra Therapeutics	Aldehyde inhibitor	Tranquility failed; Tranquility-2 modified, data due mid-2022
HL036	Hanall Biopharma/Daewoong Pharmaceutical/Harbor Biomed	TNFa inhibitor	Velos-2 failed in Jan 2020 but showed some benefits; Velos-3 completes Jul 2022; China study completes Feb 2022
ALY688 Ophthalmic Solution	Allysta Pharmaceuticals	Adiponectin receptor agonist	Ph2/3 Oasis-1 completes Mar 2022
Tivanisiran	Pharmamar	RNAi eye drop inhibiting TRPV-1	SYL1001 _V study in dry eye with Sjögren's Syndrome completes Apr 2022
BRM421	Brim Biotechnology	Synthetic peptide	Ph2/3 data reported Jun 2021; ph3 to start 2022
AR-15512	Aerie Pharmaceuticals	TRPM8 agonist	Ph2b Comet-1 failed, ph3 to begin H1 2022

Source: Evaluate Pharma & clinicaltrials.gov.