Evaluate Vantage

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Proqr hopes to usherin a new ophthalmic therapy

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The group's antisense project is the only game in town for Usher syndrome, but its latest trial is not a slam-dunk.

Mixed mid-stage data on Proqr's exon skipper QR-421a in the rare ophthalmic disorder Usher syndrome were released early on Wednesday morning to widespread apathy. Yesterday, however, the company's stock shot up 61%. It is not clear why this reaction was delayed.

Neither is it clear that it was justified. The phase 1/2 data are apparently enough for Proqr to push ahead with pivotal studies, but they are not wildly positive, and the number of patients is small. There is one thing in the company's favour, however: should phase 3 show a more definite benefit, Proqr looks likely to have the Usher's market to itself for some time.

The phase 1/2 Stellar trial saw 14 patients with Usher syndrome and non-syndromic retinitis pigmentosa due to exon 13 mutations in the *USH2A* gene receive Proqr's intravitreous antisense oligonucleotide, and six receive a sham injection. Skipping the mutated exon should allow production of a shorter but still functional form of usherin, a protein necessary for the development of the inner ear and retina.

In the trial subjects with advanced disease the primary measure of efficacy was best corrected visual acuity. In all 14 treated patients a mean benefit of 6.0 letters was seen in the treated compared with untreated eyes 48 weeks after a single injection. In the six with advanced disease the mean benefit in the treated versus untreated eyes was 9.3 letters at week 48.

According to Evercore ISI analysts, a three-line gain on the standard chart used for BCVA is considered clinically meaningful by the FDA. Since there are five letters in each line on the chart, Stellar appears to have missed this threshold. It is close to meeting the EMA's requirement for meaningfulness, however, at least in the advanced patient cohort: the EU agency has set this at a gain of two lines.

Sirius business

In early to moderate patients Stellar's primary efficacy goal was measurement of visual fields by static perimetry – a way of assessing vision in the peripheral retina, measured in decibels. In these eight patients, up to a mean of 13 retinal locations in the treated eyes improved by at least 7dB, versus seven locations for the untreated eyes at the same time point.

Evercore ISI analysts state that an increase of at least 7dB in five locations is considered clinically meaningful,

and a registerable endpoint. The eyes treated with QR-421a hit this target; unfortunately, so did the untreated eyes. There were no serious adverse events and no inflammation in Stellar.

Proqr by the end of the year plans to put QR-421a into two parallel pivotal phase 2/3 trials: Celeste, in patients with early to moderate disease, and Sirius, in advanced patients.

Both trials are expected to last for two years, meaning data are unlikely to appear before 2024. But Proqr is still in a dominant position in Usher. Around 16,000 people worldwide have the exon 13 mutation form of the disease, and there are no treatments.

The competition

The only other project in active clinical development specifically for Usher syndrome – excluding lapsed trials, natural history studies and academic work – appears to be a form of N-acetylcysteine amide under investigation by the Texan group Nacuity Pharmaceuticals. The Slo-RP trial compares an oral therapy, NPI-001, versus placebo in 48 patients with retinitis pigmentosa associated with Usher syndrome.

The endpoint, change in retinal sensitivity assessed by microperimetry, will be evaluated after two years' treatment, and data could come in late 2023 – just before Proqr's pivotal data might emerge.

A project known as UshStat or SAR421869, licensed by Sanofi from Oxford Biomedica, was discontinued two years ago while still in phase 2 (*Sanofi does a spring clean, February 7, 2019*).

There is some preclinical activity: Editas has a programme in Usher syndrome 2a, EDIT-102, which uses Crispr to edit exon 13 to restore healthy USH2A protein expression. It is not clear when human trials might start. Proqr has a clear runway – but phase 3 findings might have to be more convincing than Stellar.

The Usher syndrome landscape

Project	Mechanism	Company	Trial details	N	Data
Phase 2/3					
QR-421a	Exon-skipping oligonucleotide	Proqr	Sirius: sham-controlled, 24mth, multiple-dose study in advanced Usher and nsRP due to USH2A exon 13 mutations	100	Expected 2024
QR-421a	Exon-skipping oligonucleotide	Proqr	Celeste: sham-controlled, 24-month, multiple-dose study in early-moderate Usher and nsRP due to USH2A exon 13 mutations	100	Expected 2024
Phase 1/2					
QR-421a	Exon-skipping oligonucleotide	Proqr	Stellar: sham-controlled trial of QR-421a in subjects with Usher and nsRP due to USH2A exon 13 mutations	18	Mixed results
NPI-001	Antioxidant	Nacuity	Slo-RP: placebo-controlled trial in RP associated with Usher syndrome	48	Expected 2023
Preclinical					
EDIT-102	Crispr therapeutic	Editas	-	-	-

nsRP = non-syndromic retinitis pigmentosa. Source: Evaluate Pharma & clinicaltrials.gov.