Evaluate Vantage

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Proqr eyes its first big test

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With pivotal sepofarsen data due, the group will hope to get one up on Editas.

Despite being an ultra-rare disease, Leber's congenital amaurosis type 10 (LCA10), a form of inherited blindness, has attracted both Proqr Therapeutics and Editas Medicine. The latter stumbled last year, and Proqr will hope to do better with its lead project, sepofarsen, on which pivotal data are due this quarter.

These results, from the phase 2/3 Illuminate trial of sepofarsen, are important in their own right. But given the small size of the LCA10 market they are perhaps just as vital in validating Proqr's whole approach, which is based on intravitreally injected antisense oligonucleotides for various inherited retinal diseases.

Stifel analysts put peak sepofarsen sales at €300m ($339m), but estimate that Proqr's next most-advanced project, QR-421a for Usher syndrome, could peak at €1.6bn.

Project	Sepofarsen
Company	Proqr Therapeutics
Market cap	$552m
Product NPV	$338m
% of market cap	61%
Event type	Data from ph2/3 Illuminate trial
Indication	Leber's congenital amaurosis type 10
Date	Q1 2022
Trial ID	NCT03913143

With sepofarsen, Proqr is taking aim at a specific mutation in the *CEP290* gene that causes LCA10; the antisense project is designed to enable correct splicing and production of the CEP290 protein.

Editas targets the same mutation with its project, EDIT-101, but using subretinally delivered Crispr-Cas9 in vivo

gene editing. These different approaches have come about because the *CEP290* gene is too large to be packaged into an AAV vector, ruling out a more conventional gene therapy approach.

Let there be light

In Illuminate Proqr hopes to show a statistically significant improvement with sepofarsen over sham injection in mean change in best corrected visual acuity at 12 months. This seems straightforward enough, but the fact that there are two sepofarsen dosing arms in the trial could complicate matters.

The lower of the two, an 80µg loading and a 40µg maintenance dose, has been included as another control arm, Proqr's chief executive officer, Daniel de Boer, told *Evaluate Vantage*: "But that dose may actually be active – that could give us upside to this trial, because if both doses are positive that would give us more flexibility with the label."

He also said Proqr could pool the two doses to show activity versus sham, though it is hard to see such an approach being statistically significant, given trial powering constraints. Either way, such an outcome could be a sign of less-than-impressive efficacy with the high dose, 160µg loading plus 80µg maintenance.

Mr de Boer highlighted the importance of also getting a clinically meaningful result in Illuminate, but it is not entirely clear what this would entail. "There's a bit of a debate about that. In Europe they typically look at two lines as clinically meaningful; in the US it's three lines." This would correspond to a 0.2logMar or 0.3logMar improvement in BCVA respectively.

The signs for sepofarsen are promising: a phase 1/2 study found a 0.55logMar improvement in BCVA at 12 months, across all doses tested. This rose to 0.93logMar in those receiving the 160µg/80µg dose.

However, there were only 11 patients in the study and just six received the 160µg/80µg regimen. And the study did not include a sham arm, instead using patients' untreated eyes as a control.

Eye charts

A final issue to look out for in Illuminate will be how vision is evaluated. The best-established measure is the ETDRS, the standard letter eye chart seen in optician's offices. However, some patients cannot even read the largest letters on this chart; for them other tests have been developed, such as the Berkeley rudimentary vision test, which uses stripes and shapes.

The BRVT is less well established; however, Mr de Boer said the "vast majority" – around 90% – of patients in Illuminate would be evaluated using the ETDRS.

Proqr hopes that one study will be enough for approval, given the ultra-rare nature of LCA10 and the precedent set by Roche's Luxturna. Proqr is enrolling patients aged under eight in a second pivotal trial, Brighten, but that is primarily evaluating safety.

Unlike Luxturna, sepofarsen is not a once-and-done therapy: the Proqr project is given every six months. Should Illuminate succeed, this would likely be an acceptable schedule given the lack of other options for LCA10.