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Upcoming events – Nightstar's gene therapy and Alnylam's givosiran await key readouts

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Nightstar hopes that early gene therapy data will give it a spark, while Alnylam awaits pivotal results for one of its biggest pipeline prospects, givosiran.

Welcome to your weekly digest of approaching regulatory and clinical readouts. Although gene therapy approaches are still in their infancy, the potential of a "once and done" treatment means that all updates in the field are watched with interest. The UK group Nightstar will soon come under the spotlight with preliminary phase I/II results for NSR-RPGR, its X-linked retinitis pigmentosa candidate, due at the Euretina 2018 conference on September 22.

The focus of the 15-patient Xirius trial of NSR-RPGR, which uses the AAV8 vector to transport optimised human retinitis pigmentosa GTPase regulator (RPGR) DNA into the patient's eye, will be safety.

But investors will also be looking for improvements in retinal sensitivity, the amount of light perceived in specific parts of the retina. And with an expansion study planned for the fourth quarter, any dose-escalation effects from the five different cohorts in the trial will also be examined closely.

X-linked retinitis pigmentosa is a rare inherited disorder that primarily affects boys and is characterised by mutations in the *RPGR* gene, which causes the loss of photoreceptors, the cells responsible for converting light into visual signals. XLRP sufferers typically experience increasing symptoms of night blindness, leading to a loss of peripheral vision and then full vision by the age of around 40.

Several other companies are developing gene therapies for retinitis pigmentosa, and there are also cell therapies in development, such as Reneuron's ReN003 (*Deal hopes revive Reneuron, July 11, 2018*). Still, Nightstar is ahead, with even the most advanced of its competitors not due to report data until next year.

Even if Xirius is a success, however, NSR-RPGR could still face obstacles. Spark's Luxturna, the first gene therapy for a rare eye disease, might have blazed a trail with its approval in retinal dystrophy, but the reimbursement landscape for novel gene therapies is still in its infancy, and payment terms remain uncertain.

Nightstar might need a more experienced partner to navigate these largely uncharted waters. If Xirius reads out positively it could give it more options here.

Selected therapies in clinical development for retinitis pigmentosa				
Project	**Company**	**Description**	**Trial ID**	**Data due**
Phase II				
jCell	Jcyte	Stem cell therapy	NCT03073733	2019
Phase I/II				
NSR-RPGR	Nightstar Therapeutics	RPGR gene therapy	Xirius, NCT03116113	Feb 2019
ReN003	Reneuron	Stem cell therapy	NCT02464436	2019
RST-001	Allergan	ChR2 gene therapy	NCT02556736	2019
AAV-RPGR	Meiragtx	RPGR gene therapy	NCT03252847	2020
HORA-PDE-6B	Horama	PDE6B gene therapy	NCT03328130	2020
BIIB088	Biogen/Applied Genetic Technologies	RPGR gene therapy	NCT03314207 NCT03316560	2021, 2022
Source: EvaluatePharma.				

Alnylam is also targeting an ultra-rare disease, acute hepatic porphyrias, with its subcutaneously delivered RNA interference candidate givosiran, which could become its second marketed product after the recently approved Onpattro, the first RNAi therapy to be greenlit.

Givosiran's future hinges on results of the Envision trial, topline results of which will be available by the end of this month. The primary endpoint is the annualised rate of porphyria attacks over six months, but initial data will involve a biomarker, urinary aminolevulinic acid, which Alnylam hopes will be enough to support accelerated approval.

The company has talked up acute hepatic porphyrias as the equivalent of hereditary angioedema, which has defied early expectations to become a $1.6bn market. At present the only available treatment for acute hepatic porphyrias is hematin, which must be given via intravenous infusion.

Givosiran works by preventing the translation of the ALAS1 protein, which in turn lowers levels of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). Elevated levels of these two products causes acute neurovisceral attacks, characterised by severe pain, changes in heart rate or blood pressure, vomiting and sweating, which often put patients in hospital.

Analysts have so far been positive about givosiran, given that in previous trials the treatment has been able to reduce levels of urinary ALA by over 70%, earning it a breakthrough therapy designation. The only potential fly in the ointment for Alnylam might be the relatively small amount of safety data, but in clinical trials there have been no imbalances in serious adverse events.

If the Envision results are positive Alnylam plans to file givosiran by the end of the year, with approval expected in 2019, a year ahead of schedule. The project could bring in $446m in 2024, according to consensus sellside forecasts from *EvaluatePharma.* If Alnylam's hopes come true this could well rise.

Study	Trial ID
Envision	NCT03338816

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