Health Technology Briefing
March 2023

Botaretigene sparoparvovec for treating X-linked retinitis pigmentosa

Company/Developer	Janssen UK

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28922	NICE ID: 10592	UKPS ID: 659553

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Botaretigene sparoparvovec is in development for the treatment of X-linked retinitis pigmentosa. Retinitis Pigmentosa (RP) is an inherited eye condition that affects the cells that line the back of the eye in the region known as the retina. RP is one of the most complicated genetic conditions, and over 80 causative genes have been identified. X-linked RP is caused by a defect in a gene called RPGR which is located on the X-chromosome. Symptoms initially include difficulty seeing in dim light, including transitioning from light to dark and vice versa. Peripheral vision will also decline, resulting in a narrowing of the visual field and, in some cases, resulting in complete blindness. There are currently no approved treatments that can effectively slow or stop the progression of X-linked RP.

Botaretigene sparoparvovec is a gene therapy which is designed to deliver copies of a gene called RPGR to cells in the retina. The eye-specific form of this gene is required by cells in the eye for them to function and delivering this gene aims to counteract the loss of retinal cells to preserve and restore vision. Botaretigene sparoparvovec has been shown to be safe and effective in early-stage clinical trials and is administered subretinally. If licenced, botaretigene sparoparvovec will become the first approved treatment option for patients with X-linked RP caused by mutations in the RPGR gene.

Proposed Indication

The treatment of patients with confirmed Retinitis Pigmentosa GTPase Gene Regulator (RPGR) mutation-associated X-linked retinitis pigmentosa (RP).[1]

Technology

Description

Botaretigene sparoparvovec (AAV-RPGR) is a gene therapy designed to treat the most common form of X-linked RP caused by mutations in the eye-specific form of the RPGR gene called RPGR open reading frame 15 (RPGR ORF15). Both rods and cones photoreceptors require RPGR ORF15 to function.[2] It is designed to deliver functional copies of the RPGR gene to counteract the loss of retinal cells with the goal of preserving and potentially restoring vision for those living with X-linked RP.[3]

Botaretigene sparoparvovec is currently in clinical development for the treatment of X-linked RP. In the phase III clinical trial (NCT04671433) participants are given bilateral, subretinal botaretigene sparoparvovec.[1]

Key Innovation

There are currently no treatments that can effectively slow or stop the progression of X-linked RP.[4] In the phase I/II trial (NCT03252847) treatment with botaretigene sparoparvovec in patients with X-linked RP was found to have an acceptable safety profile and efficacy assessments in this proof-of-concept study demonstrated improvements in retinal sensitivity, visual function and functional vision.[5]

Botaretigene sparoparvovec is an advanced therapy medicinal product (ATMP) within the definition of a gene therapy medicine. The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).[6] If licenced, botaretigene sparoparvovec will become the first approved treatment option for patients with X-linked RP.

Regulatory & Development Status

Botaretigene sparoparvovec does not currently have Marketing Authorisation in the EU/UK for any indication.

Botaretigene sparoparvovec is not currently in phase II or phase III trials for any other indication.[7]

Botaretigene sparoparvovec has been awarded the following regulatory designations:

- An orphan drug in the EU in 2016 for the treatment of RP[8]
- A PRIME status for the treatment of inherited retinal disease X-linked RP by the EMA in February 2020[9]
- A Fast Track by the US FDA for the treatment of X-linked RP in April 2018[10]

Patient Group

Disease Area and Clinical Need

RP is an inherited eye condition that affects the photoreceptor cells responsible for capturing images from the visual field. These cells line the back of the eye in the region known as the retina. RP is one of the most complicated genetic conditions, and over 80 causative genes have been identified. Rod cells are usually

initially involved, and difficulty seeing in dim light, including transitioning from light to dark and vice versa, is one of the earliest symptoms. Peripheral vision will also decline, resulting in a narrowing of the visual field. Central vision is often maintained until much later.[4] Symptoms usually start in childhood, and most people eventually lose most of their sight.[11] X-linked RP is caused by a defect in the RPGR gene which is located on the X-chromosome, and this is why the disease affects men and women differently. Women have two X-chromosomes and so a normal RPGR gene on one X-chromosome can compensate for a defective RPGR gene on the other X-chromosome to some extent. Men, however, only have one X-chromosome.[12] This means X-linked RP predominantly affects males. However, some female carriers may also be clinically affected, although usually with a much less severe phenotype than males.[13]

RP presents multiple modes of inheritance and 10–15% are X-linked. Linkage studies suggest that RPGR accounts for 70–90% of X-linked RP.[14] RP is the most common retinal dystrophy affecting 1 in 4,000 individuals.[15] In England, 2021-22, there were 125 finished consultant episodes (FCEs) and 124 admissions for hereditary retinal dystrophy (ICD-10 code H35.5) which resulted in 58 FCE bed days and 90 day cases.[16] The population likely to be eligible to receive botaretigene sparoparvovec could not be estimated from available published sources.

Recommended Treatment Options
There are currently no approved pharmacological treatment options for X-linked RP.[17,18]

Clinical Trial Information

Trial	NCT03252847, EudraCT 2016-003967-21; An Open Label, Multi-centre, Phase I/II Dose Escalation Trial of a Recombinant Adeno-associated Virus Vector (AAV2-.RPGR) for Gene Therapy of Adults and Children With X-linked Retinitis Pigmentosa Owing to Defects in Retinitis Pigmentosa GTPase Regulator (RPGR) **Phase I/II** – Completed **Locations:** UK and USA **Study completion date:** November 2021	NCT04312672, EudraCT 2018-000425-31; Long term follow-up study of participants following an open label, multicentre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV2/5-hRKp.RPGR) for gene therapy of adults and children with X-linked Retinitis Pigmentosa owing to defects in Retinitis Pigmentosa GTPase Regulator (RPGR) **Phase I/II** – Recruiting **Locations:** UK and USA **Primary completion date:** June 2023
Trial Design	Randomised, sequential assignment, open-label	Observational, cohort, prospective
Population	N=49 (actual); Have X-linked retinitis pigmentosa confirmed by a retinal specialist; Aged 5 years or older male	N=36 (estimated); Received AAV2-RPGR in the MGT009 study (NCT03252847); Aged 5 years or older male
Intervention(s)	• Part 1, dose escalation: One of three doses of single, subretinal AAV2/5-RPGR	No intervention (follow-up study)

	• Part 2, expansion: One of two doses of single, subretinal AAV2/5-RPGR	
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome measure: • Incidence of adverse events related to the sub retinal administration of AAV2-RPGR [Time frame: 18 months] See trial record for full list of other outcomes	Primary outcome measure: • Assess the long-term safety of AAV2-RPGR vector administered in the MGT009 (NCT03252847) trial [Time frame: 60 months] See trial record for full list of other outcomes
Results (efficacy)	Analyses of the pooled low and intermediate dose cohorts demonstrated improvement in retinal sensitivity in the treated eyes compared to untreated eyes in the randomised concurrent control arm as measured by both full-field static perimetry and microperimetry. An improvement in mean retinal sensitivity as measured by static perimetry in the central 10-degree area of the retina was observed at six months in the treated eye compared to untreated eyes in the randomised concurrent control arm [in the full analysis of pooled low and intermediate doses across adults: 1.96 decibel (dB); (±95% CI: 0.59, 3.34); and in the sensitivity analysis when applying the Phase 3 criteria: 2.42 (0.91, 3.93)].[5]	-
Results (safety)	Botaretigene sparoparvovec demonstrated an adverse event (AE) profile that was anticipated and manageable. Most AEs were related to the surgical delivery procedure, were transient and resolved without intervention. There were no dose-limiting events. A total of three serious adverse events (SAEs) were observed in the overall trial; two SAEs, which were previously reported, were observed in the dose-escalation phase of the study (n=10; one retinal	-

	detachment and one panuveitis in the low dose cohort), and a single additional SAE of increased intraocular pressure was observed in the dose escalation phase and resolved with treatment.[5]	

Trial	NCT04671433, EudraCT 2020-002873-88; Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene **Phase III** – Recruiting **Locations:** Four EU countries, UK, USA, Israel and Switzerland **Primary completion date:** March 2024	NCT04794101, EudraCT 2020-002255-37; Follow-up Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene **Phase III** – Recruiting **Locations:** Four EU countries, UK, USA, Israel and Switzerland **Primary completion date:** May 2029
Trial Design	Randomised, parallel assignment, single-blinded	Randomised, parallel assignment, single-blinded
Population	N=96 (estimated); Has XLRP confirmed by a retinal specialist and has a predicted disease-causing sequence variant in RPGR confirmed by an accredited laboratory; Aged 3 years or older	N=96 (estimated); Has XLRP confirmed by a retinal specialist and has a predicted disease-causing sequence variant in RPGR confirmed by an accredited laboratory; Aged 3 years or older
Intervention(s)	AAV5-RPGR (subretinal)	Deferred treatment from NCT04671433 (subretinal AAV5-RPGR)
Comparator(s)	No comparator (deferred treatment)	No comparator (already treated)
Outcome(s)	Primary outcome measure: • Change from baseline to week 52 in vision-guided mobility assessment (VMA) as measured by the ability of the participant to navigate through a VMA maze [Time frame: 52 weeks] See trial record for full list of other outcomes	Primary outcome measures: • Change from baseline in vision-guided mobility assessment (VMA), as measured by the ability of the participant to navigate through a VMA maze, after bilateral subretinal delivery of AAV5-hRKp.RPGR [Time frame: day 1 – month 60] • Safety and tolerability of bilateral treatment through month 60 [Time frame: day 1 – month 60] See trial record for full list of other outcomes

Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

The cost of botaretigene sparoparvovec is not yet known.

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Insertion of a subretinal prosthesis system for retinitis pigmentosa (IPG537). December 2015.
- NICE interventional procedures guidance. Insertion of an epiretinal prosthesis for retinitis pigmentosa (IPG519). June 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Argus II retinal prosthesis for retinitis pigmentosa. 16027/P. July 2016.

Other Guidance

- British Medical Journal Best Practice. Retinitis Pigmentosa. 2022.[19]

Additional Information

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