Information for the public

related to the Genetically Modified Organism (GMO)

Application submitted in Belgium for the use of AAVB-039; Dual AAV8.ABCA4

in Clinical Trial 039-101

EU Trial Number	2025-522207-15-01
Investigational Medicinal Product	AAVB-039; Dual AAV8.ABCA4
Study Number	039-101
Study Title	An Open-label, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1) (CELESTE)
Lay Protocol Title	An Open-label, Multicenter Trial to Assess Safety and Efficacy of a Subretinal Administration of AAVB-039
Study Phase	Phase 1/2
Sponsor	AAVantgarde Bio UK Ltd., Victoria House, Bloomsbury Square, London, WC1B 4DA, England

1. Description of the Genetically Modified Organism (GMO)

AAVB-039 is a dual AAV8.ABCA4 gene replacement therapy for the production of functional human ABCA4 protein. As the coding DNA sequence (CDS) for ABCA4 is too large to be packaged into a single adeno associated viral (AAV) vector, AAVB-039 utilizes a dual AAV vector approach, which overcomes the packaging capacity limit of individual AAV vectors (<5 kb) to allow the delivery of larger CDSs, by splitting the CDS in two separate vectors made as individual drug substances, AAV8.5'ABCA4.N-intein (N-ter DS) and AAV8.3'ABCA4.C-intein (C-ter DS), which are combined into a single drug product (AAVB-039). AAVB-039 is manufactured in accordance with current good manufacturing practices using HEK293 cells and plasmids as starting materials.

2. Nature and goal of the foreseen deliberate release

The nature of the release is for clinical trial use only. All patients will receive a single subretinal administration of AAVB-0039. This subretinal injection will be performed as

a procedure in an operating room. The subretinal injection procedure will be performed on Day 0. The goal of the clinical trial is to determine the safety and tolerability of AAVB-039 per trial protocol.

3. Framework of research and/or development

STGD1 is an autosomal recessive retinopathy caused by mutations in the retina-specific ATP-binding cassette (ABC) transporter gene (ABCA4) located on chromosome 1. STGD1 is an inherited retinal disease (IRD), frequently quoted in literature as estimated to affect approximately 1 in 8,000 to 10,000 individuals. A much higher prevalence (1:6,578 to 1:870) has been estimated in genetic studies based on ABCA4 mutation carrier frequencies but do not correlate to the observed disease prevalence. An accurate prevalence of ABCA4-related STGD1 is difficult to estimate due to its substantial phenotypic and genotypic heterogeneity (Cremers 2020). The age of onset and rate of progression varies greatly where central vision loss typically manifests in early childhood and young adulthood, but some individuals may present later in Adulthood.

The research will be conducted in Study 039-101, a Phase 1/2, open label, ascending dose followed by a controlled trial. The study is conducted in accordance with local laws and regulations and applicable EU clinical trial legislation.

a. Objective

The main goals of the study are:

- To determine the safety, tolerability and a preferred dose level of AAVB-039; and
- To determine efficacy of AAVB-039 at the preferred dose level.

b. Trial design

This is a Phase 1/2 Study, Open-label, Multicenter, Two Part, Ascending Dose Followed by a Controlled Trial to Assess the Safety and Efficacy of a Subretinal Administration of AAVB-039 in Participants with Stargardt Disease (STGD1).

c. Trial population

This study will include patients with confirmed Stargardt disease. Approximately 75 eligible participants will be enrolled globally.

4. Potential advantages of the deliberate release

Given the lack of available therapies, there is an unmet medical need in patients with STGD1. Non-clinical pharmacology studies have shown that a single subretinal administration of AAVB-039 can reconstitute the full-length human ABCA4 protein in the retina of both small and large animals, including cynomolgus macaques, whose eye is very similar to the human eye in terms of size, architecture, and the presence of a macula.

5. Assessment of the potential risks for human health and the environment linked to the deliberate release

The main risks of treatment with the subretinal administration itself may cause inflammation, as consequence of the surgical procedure and it is usually managed with corticosteroid treatment. This effect has been observed in macaque eyes receiving either the vehicle control article or AAVB-039. Procedure-related findings were comparable between groups (elevated dose sites, conjunctival hyperemia, small focal retinal or subretinal hemorrhage, red vitreous floaters hemorrhage at the site of dose administration) and either resolved without complication or improved considerably through the study. Also, various levels of aqueous cells and flare and vitreous cells were observed. These tended to rapidly subside in eyes administered the vehicle control, while in AAVB-039 treated eyes, they persisted longer in a dose dependent manner, improving over time with only mild levels of vitreous cells finally observed in AAVB-039 treated eyes at Week 13 and residual levels observed in one animal per dose level at the end of the study. Signs of posterior segment inflammation (e.g. perivascular sheathing and grey-to-white subretinal choroidal foci) were also observed in eyes receiving AAVB-039 (mainly high-dose treated eyes) and were managed successfully with corticosteroids. Overall anterior and posterior inflammation was controlled with anti-inflammatory therapy.

AAV gene therapy is unable to replicate given the design of the construct. Therefore, potential risk for human health and the environment linked to the deliberate release is considered low.

6. Proposed measures to limit the potential risks, to control and to ensure follow-up of the deliberate release

Healthcare providers and study personnel will be trained in best safety practices to be applied during handling, administration and disposal of AAVB-039. Given the route of administration, the IMP will not leave the hospital and will be stored and prepared in the hospital pharmacy prior to administration in the surgical suite.

Healthcare professionals will wear protective clothing when administering treatment, will have adequate equipment available to clean up any spills safely, and will properly dispose of medical waste.

AAVB-039 will be shipped to trial sites in line with standard recommendations for the safe transport of experimental gene therapies. All study treatments must be stored in a secure and monitored area in accordance with the labelled storage conditions, with access limited to authorized site staff.

7. Conduct of the study in Belgium

a. Participating sites in Belgium:

Organisation Name:	Universitair ziekenhuis Gent (Ghent University Hospital)
Address Details:	Corneel Heymanslaan 10, 9000 Ghent (Belgium)
Contact person:	Bart Peter Leroy, MD, PhD Email : (Bart.leroy@uzgent.be). Tel: +32 9 332 63 44

Expected number of patients that will be enrolled in Belgium: 3

Expected start date of the study in Belgium: 19May2026

Expected end date of the study in Belgium: 19May2032