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Abstract Title: Transferrin in geographic atrophy patients using non-viral ocular gene therapy : safety, tolerability and early efficacy results from PST-611-CT1, a first-in-human trial.

Abstract Topic: Age-related Macular Degeneration (AMD) / Central Serous Chorioretinopathy (CSC)

Abstract Subtopic: Novel Therapies

Preferred Presentation Type: Late Breaking Abstract

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Purpose

Growing evidence identifies iron overload as a key factor in age-related macular degeneration progression. Supplementation of transferrin in the eye is a novel therapeutic approach to restore iron homeostasis and prevent oxidative stress, inflammation, and ferroptosis related to iron overload. Herein we present emerging efficacy results from a first-in-human trial with PST-611, a non-viral gene therapy administered using the PulseSight electrotransfection system that induces the ciliary muscle to express transferrin.

Setting/Venue

PulseSight Therapeutics, Paris, France

Centre de Recherche des Cordeliers, Paris, France

Ophtalmopôle, Assistance Publique - Hôpitaux de Paris, Paris, France

Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France.

Methods

This first-in-human, Phase 1, open-label, single-ascending-dose trial (NCT07024732, 2024-519025-37-00 and 2025-A00042-47) enrolled patients with geographic atrophy (GA). A single low and high dose of PST-611 have been administered sequentially in the study eyes of 2 successive dose groups of participants in a conventional 3+3 dose escalation regimen. The decision to administer the high dose was based on adequate safety and tolerability of the low dose at 2 weeks post-dose. Participants were followed up for a total of 16 weeks post-dose. Safety and tolerability assessments included full ophthalmological examination, ocular and systemic adverse event (AE) collection, BCVA (ETDRS letters) and SD-OCT imaging.

Upon spontaneous participant feedback on improved vision in the study eye during daily activities, as well as clinically observable inflections of GA growth dynamics on SD-OCT, a deep learning-based segmentation of SD-OCT was performed to evaluate the change over time of the area of retinal pigment epithelium (RPE) depletion (i.e., the GA area) and of the area of photoreceptor depletion, measured as the combined depletion of the Ellipsoid Zone (EZ), the Outer Photoreceptor Segment (OPR) and the Interdigitation Zone (IZ).

Results

PST-611 has been administered to a total of 6 participants, 3 in the low dose group and 3 in the high dose group. All 6 participants completed the trial. In all participants, PST-611 demonstrated a favorable safety

profile, with no dose-limiting or serious adverse events reported. The most commonly reported AE was conjunctival hyperemia. No clinically relevant findings have been reported at full ophthalmological examination and on SD-OCT. BCVA was stable over the 16 weeks of follow-up. Both, the low and the high dose, were identified as safe and well tolerated.

On SD-OCT deep learning-based segmentation, in the study eye of 5 out of 6 participants, 2 in the low dose group and 3 in the high dose group, a reduction of 30% to over 50% of the growth rates of the RPE depletion areas and the photoreceptor depletion areas was observed after PST-611 administration, as compared to the corresponding growth rates reported in the same eyes prior to PST-611 administration. No relevant changes in these growth rates were observed in the 5 evaluable non-treated eyes.

Conclusion

PST-611 is well tolerated, with no dose-limiting or serious adverse events reported and BCVA was stable over the duration of the follow-up. Although unexpected in a first-in-human single dose trial with only 16 weeks of follow-up, the observed significant reduction in the growth rates of RPE depletion areas and photoreceptor depletion areas after PST-611 administration, in the study eye of the majority of trial participants, is supported by the role of transferrin in the eye and is aligned with the suspected role of iron overload and ferroptosis in the pathogenesis and progression of GA. These results support continued development of PST-611 in GA and the conduct of a repeat-dose Phase 2 clinical trial with the high PST-611 dose.

Financial Disclosures: Yes Consultant Chief Medical Officer for PulseSight Therapeutics

Is this the first presentation of results of a major clinical trial? No

YOURS membership: No

Occupation of Presenting Author: Researcher