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Corresponding author(s): José-Alain Sahel and Botond Roska

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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All EEG data were collected by the EEGO v1.9.1 software and Arduino custom code for data acquisition (software Processing version 3.5.4). The code for EEG data processing and spectral analysis is available at the following URL: https://github.com/JBDSA/OptoRehabEEG
Data analysis	Analyses of behavioral data were conducted in R, version 4.0.3.. EEG data were preprocessed and analyzed using the EEGLAB toolbox version 14.1.0 in MATLAB (versions R2019a & R2020a), ICLabel version 1.2.6 using the default option (EEGLAB plug-in), and MATLAB custom code. Statistical analyses of EEG data were conducted in JASP, version 0.11.1.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All requests for raw and analyzed data are promptly reviewed by Gensight Biologics to verify if the request is subject to any intellectual property or confidentiality obligations. Patient-related data not included in the paper were generated as part of clinical trials and may be subject to patient confidentiality. Any data that can be shared will be released via a Material Transfer Agreement. All raw and analyzed image data can be found at: https://passageinnovation-my.sharepoint.com/:f:/g/personal/mtaiel_gensight-biologics_com/EkUITiEa4AxNs_YryLq7fT8BGpdYkXZMWWtDK6Wg-fcQfA

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No formal statistical hypothesis or sample size estimation were established for the PIONEER study. The sample size follows the traditional 3 + 3 dose escalation design for the 3 dose levels (Vignal C et al. Safety of rAAV2/2-ND4 Gene Therapy for Leber Hereditary Optic Neuropathy. Ophthalmology. 2018 Jun;125(6):945-947. doi: 10.1016/j.ophtha.2017.12.036.). Sample size of PIONEER is consistent with previous early phase studies of gene therapy in orphan indications (Maguire AM et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet. 2009 Nov 7;374(9701):1597-605. doi: 10.1016/S0140-6736(09)61836-5).
Data exclusions	No data were excluded from the analyses.
Replication	The first visual test "finding notebook or staple box" included a total of 40 randomized notebook/staple box with three contrasts replicate trials distributed across three conditions: natural binocular, natural monocular, and stimulated monocular (6, 6, and 28 trials, respectively). The second visual test "counting tumblers and locating them" test included a total of 25 randomized 2 objects/3objects with three contrasts replicate trials distributed across three conditions: natural binocular, natural monocular, and stimulated monocular (3, 3, and 19 trials, respectively). The visual detection task coupled with EEG recordings included a total of 183 randomized object/no-object replicate trials distributed across three conditions: natural binocular, natural monocular, and stimulated monocular (60, 60, and 63 trials, respectively).
Randomization	No randomization scheme was applied to treatment allocation. The patient's worse-seeing eye was selected for treatment with combined GS030 therapy.
Blinding	Not applicable, as this is an open-label study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Study participants have non-syndromic late-stage retinitis pigmentosa (RP), are between 18 and 75 years of age, mixed gender, and have at most Light Perception vision in their worse-seeing eye. The reported male patient is 58 years old and has two pathogenic alleles on the USH2A gene (NM_206933.2) that were identified by targeted next-generation sequencing (Audo et al., 2012) and segregation analysis using samples from his parents. The first pathogenic allele is on exon 13: c.2299del p.(Glu767Serfs*21) (Eudy et al., 1998), inherited from his father. The second pathogenic allele is a complex allele with exon 22 c.4714C>T p.Leu1572Phe (Song et al., 2011) and exon 50 c.9882C>G p.Cys3294Trp (Nishiguchi et al., 2013), inherited from his mother.
Recruitment	Participants in the PIONEER study are selected by study investigators according to the protocol selection criteria. They have to sign a detailed informed consent form before study enrollment, as per Good Clinical Practice and local regulations. The participation to the study was proposed to all patients who fulfilled the inclusion criteria across the three centers and there was no bias in the study recruitment.

Ethics oversight	Before study initiation, the PIONEER study protocol was approved by Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM, France), the US Federal Drug and Food Administration (FDA, USA), the Medicines and Healthcare products Regulatory Agency (MRHA, UK); and the following national/local ethic committees and institutional review board: Comité de Protection des Personnes [CPP] Île-de-France III, France; North-East York Research Ethics Committee (REC), UK; Human Research Protection Office (HRPO) at the University of Pittsburg, Pittsburg, USA.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03326336
Study protocol	Full study protocol is available in appendix of the case report manuscript
Data collection	The PIONEER study is carried out at three investigational sites: the Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts (Paris, France), the Moorfields Eye Hospital NHS Foundation Trust (London, United Kingdom), and the Department of Ophthalmology at the University of Pittsburgh School of Medicine (Pittsburgh, USA). Patient recruitment started in September 2018 and is ongoing.
Outcomes	The primary objective of the PIONEER study is to evaluate the safety and tolerability of escalating doses of GS030-DP administered via a single IVT injection and repeated light stimulation using the GS030-MD goggles, in subjects with non-syndromic RP. The primary endpoint is assessed at Week 52/Year 1 based on local and systemic safety issues, specifically those related to IVT of GS030-DP and the subsequent repeated use of GS030-MD, as assessed by incidence of adverse events (AEs). The secondary objectives of the PIONEER study, that have been reported, are to: - Evaluate the treatment effect of GS030 combined therapy, as assessed by vision and ocular measures, including visual acuity and visual function. - Compare visual acuity and visual function before and after gene transfer, with and without GS030-MD. The reported secondary endpoints are: - Assessment of the treatment effect on visual function and functional vision, with the change from baseline to Week 52 of parameters, including visual perception tests, eye-hand coordination and visual exploration. -Assessment of the treatment effect on structural changes of the posterior pole of the fundus from baseline to Week 52 with parameters measured with SD-OCT, color fundus photography, and fundus auto fluorescence (FAF).