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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	Spectralis 6.8, Heidelberg Engineering, Germany; Espion 6.59, Diagnosis, USA; Roland Consult Ver.1017.2.0.6, Germany
Data analysis	Excel Office 365, Microsoft, USA; Sigmaplot 13.0, Systat, USA; MATLAB 2018a, Mathworks

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 relevant patient-level data are displayed in Figures 1 and 2, and Extended Data Figs 1-9. All requests for data will be reviewed by ProQR Therapeutics and the universities involved to verify whether the request is subject to any intellectual property or confidentiality obligations. Patient-related data may be subject to confidentiality. Any data that can be shared will be released.

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	We are reporting results mostly from one patient (except for the comparison to five previously published results) in an ongoing first-in-man study. The clinical trial was designed to evaluate initial safety and feasibility, and as typical in ultra-rare diseases, 11 patients were enrolled in 3 centers. Current report is on the only patient that received a single dose, as opposed to multiple doses received by all other 10 patients. No statistical method was used to predetermine sample size for this open-label non-randomized clinical trial.
Data exclusions	Pupillary recordings at months 12 and 15 were not analyzed because at those visits the patient was on sertraline with known side effects on pupillary function. This was not a pre-established exclusion criterion.
Replication	This is an early Phase first-in-man clinical trial and there was no replication. A randomized Phase 3 trial is ongoing.
Randomization	There was no randomization as this was an open label protocol.
Blinding	This is an early phase trial. Masking was not possible since there was no placebo injection, and the injected eye was obvious to both the patients as well as the evaluating investigators.

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	The patient was homozygous for c.2991+1655A>G mutations in CEP290 and a clinical diagnosis of autosomal recessive Leber congenital amaurosis (LCA). The patient was 14 years old at the time of the injection and received 160 µg sepofarsen in 50 µL.
Recruitment	Patient was recruited from the clinical practice of the physician-co-investigator. The rarity of this specific orphan disease led to this recruitment process. Enrollment only occurred if inclusion criteria were met and the patient expressed interest in participation, given full discussion of the protocol and risks. It is unknown whether there was any self-selection bias, and how such a bias may have impacted the results.
Ethics oversight	Study was approved by the University of Pennsylvania IRB. Patient provided written informed assent, and the parents provided written informed consent.

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	NCT03140969
Study protocol	Full trial protocol is available upon request from the authors.
Data collection	Patient was recruited in August 2018, and clinical trial data was collected at the Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania between August 2018 and December 2019.
Outcomes	Primary outcome was safety. Ocular safety was assessed with standard eye examinations, including gradings of the anterior and posterior segment, and of the lens. Systemic safety was evaluated with physical examinations at screening and post dosing visits. Routine hematology, serum chemistry, prothrombin time (with international normalized ratio) were performed at screening and post dosing. Secondary outcomes included visual acuity, FST, mobility, pupillometry, autofluorescence imaging and OCT imaging. Visual acuities were assessed with standard ETDRS as well as under low-luminance conditions. FST was performed with two stimulus colors under dark-adapted and light-adapted conditions. Mobility was performed under different lighting conditions. Pupillometry was evaluated with red stimuli under dark-adapted conditions. Autofluorescence imaging and OCTs were performed with near infrared lights. Details are provided in Methods.