Summary of Clinical Study Report

THOR - Tübingen Choroideremia gene therapy trial open label Phase 2 clinical trial using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)

Name of test drug/investigational product: rAAV2.REP1

Indication studied: Choroideremia

Development phase of study:
Phase II

EudraCT Number: 2014-005004-21

Protocol identification code:
THOR-TUE-01

Date of the report: 13. April 2022

Version: Version 1.0

Leiter der klinischen Prüfung (Coordinating Investigator)/Prüfer (Principle Investigator)	Sponsor
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Author Study Report
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Study initiation date (first patient enrolled, or any other verifiable definition): 23.12.2015
Date of early study termination, if any study completion date (last patient completed): 26.02.2018
The follow-up phase of the THOR study was terminated earlier, after all patients were transferred to a new observational study (Solstice, EudraCT 2017-003104-42). Solstice includes the same safety examinations like the THOR study and even additional examinations.

Unterschriften

The Authors confirm the reported content by signature. The study (including the archiving of essential documents) was performed in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable laws.
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor's delegated person	Dr. med. Tobias Peters Name, Titel	29.04.2022 Datum, Unterschrift
Principle Investigator	Prof. Dr. Dr. Dominik Fischer Name, Titel	28. April 2022 Datum Unterschrift
Other authors of study report	Dr. rer. nat. Nadine Kahle Name, Titel	29.04.2022 Datum Unterschrift

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1 Name of Sponsor/Company

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Address	Geissweg 3 72076 Tübingen
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Email	Team@stz-eyetrial.de

2 Name of Finished Product and Active Substance

Finished Product	**Active Substance**
N.A.	rAAV2.REP1

3 Individual Study Table

Not applicable

4 Title of Study

THOR - Tübingen Choroideremia gene therapy trial open label Phase 2 clinical trial using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1) (Protocol Version 2.0 of 09. November 2015)

There are no amendments.

5 Investigator and Study center

Investigator	**Study Center**
Prof. Dr. Dr. M. Dominik Fischer	Department für Augenheilkunde Elfriede-Aulhorn-Straße 7 72076 Tübingen

6 Publications

Fischer MD, Ochakovski GA, Beier B, Seitz IP, Vaheb Y, Kortuem C, Reichel FFL, Kuehlewein L, Kahle NA, Peters T, Girach A, Zrenner E, Ueffing M, MacLaren RE, Bartz-Schmidt K, Wilhelm B. CHANGES IN RETINAL SENSITIVITY AFTER GENE THERAPY IN CHOROIDEREMIA. Retina. 2020 Jan;40(1):160-168. doi: 10.1097/IAE.0000000000002360. PMID: 30308560.

Fischer MD, Ochakovski GA, Beier B, Seitz IP, Vaheb Y, Kortuem C, Reichel FFL, Kuehlewein L, Kahle NA, Peters T, Girach A, Zrenner E, Ueffing M, MacLaren RE, Bartz-Schmidt KU, Wilhelm B. Efficacy and Safety of Retinal Gene Therapy Using Adeno-Associated Virus Vector for Patients With Choroideremia: A Randomized Clinical Trial. JAMA Ophthalmol. 2019 Nov 1;137(11):1247-1254. doi: 10.1001/jamaophthalmol.2019.3278. PMID: 31465092; PMCID: PMC6865291.

7 Studied period (years)

- Date of first enrolment 11.01.2016
- Date of last completed visit of last patient: 26.02.2018
- The follow-up phase of the THOR study was terminated earlier, after all patients were transferred to a new observational study (Solstice, EudraCT 2017-003104-42). Solstice includes the same safety examinations like the THOR study and even additional examinations.

8 Phase of Development

Open label Phase II trial with a non-approved investigational product.

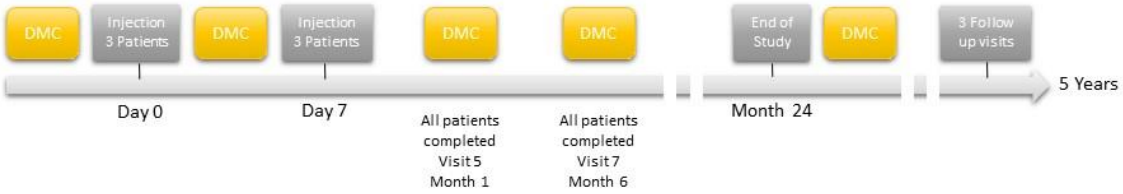
9 Objectives

The primary aim was to assess the anatomical and functional outcomes, as well as the safety of a single subretinal injection of rAAV2.REP1 in subjects with genetically confirmed choroideremia for up to 24 months.
It was predicted that the REP1 transgene would be expressed efficiently if the retinal cells survive AAV2 transduction and this would be evidenced by sustained vision.
Secondary study endpoints were change from baseline in autofluorescence evaluation, microperimetry readings and other anatomic and functional outcomes (all in the study eye compared to control eye). Secondary endpoints also included safety assessments to be conducted throughout the study. The fellow eyes of these patients were utilised as controls in this study and received no study treatment.

10 Methodology

According to protocol

- Prospektive
- Single arm study
- Open label
- If both eyes met the inclusion criteria, the randomization list was used to determine the study eye. If only one eye met the inclusion criteria, that eye became the study eye.Study eye and fellow-eye were randomized
- Schedule for data monitoring committee meetings



Points to consider for DMC

- Occurrence and nature of adverse events
- Whether additional information on adverse events is required
- Consider taking appropriate action where necessary to halt trials (see below)
- Act / advise on incidents occurring between meetings that require rapid assessment (e.g. SUSARs)

11 Number of Patients

- Planned number of cases: 6
- Subjects screened: 6
- included subjects: 6
- randomized subjects: 6
- drop-outs: 0
- subjects analyzed: 6

12 Diagnosis and Main Criteria for Inclusion

1. Genetically confirmed diagnosis of choroideremia. Patients without a confirmed mutation in the CHM gene, but who have the clinical phenotype typical of choroideremia can only be enrolled if they meet all the following three criteria: (i) family history consistent with X-linked inheritance, (ii) absent REP1 protein on Western blot of a blood sample and, (iii) normal RPE65 gene on sequencing.
2. Participant is willing and able to give informed consent for participation in the study.
3. Male aged 18 years or above.
4. Active disease visible clinically within the macula region
5. Best-corrected visual acuity equal to or worse than 6/9 (20/32; Decimal 0.63; LogMAR 0.2) but better than or equal to 6/60 (20/200; Decimal 0.1; LogMAR 1.0) in the study eye.

13 Test investigational medicinal product

Test investigational medicinal product: rAAV2.REP1
Dose: 1x10e11 vector genome particle (vgp)
Mode of administration: Single subretinal injection in study eye
Lot Number: AAV2REP10411

14 Duration of treatment

Single subretinal injection

15 Reference therapy

Reference therapy: N.A.

Dose: N.A.

Mode of administration: N.A.

Batch number: N.A.

16 Criteria for evaluation

16.1 Efficacy

- Clinical examination, including best corrected visual acuity and contrast sensitivity tested in addition to fundoscopy to check for signs of inflammation, cataract or retinal detachment.
- Anatomical assessments (fundus photography, autofluorescence and OCT scan)
- Functional tests (Goldman visual field, microperimetry, and colour vision).

16.2 Safety

- Clinical examination, including full ophthalmic examination, vital signs, blood chemistry
- Anatomical assessments: field colour fundus photography, fluorescein and indocyanine angiography
- Immunogenicity: Viral shedding, Immunoassays (anti-AAV2, anti-REP1), Immunochemistry.

17 Statistical methods

Summary statistics will be presented for both eyes (treated eye versus control eye groups). No formal statistical comparison will be performed (no p-value will be computed). For categorical/binary data, the number and proportion of patients pertaining to each category will be presented with its 95% Confidence Interval (CI). For continuous data, mean (and its 95% CI) and Standard Deviation (SD) will be presented.

The primary outcome measure will be the proportion of patients with a relative change from baseline of > 5 in ETDRS letters, when comparing a patient's treated eye versus the control eye. At each time point, the change from baseline in ETDRS letters will be computed for each eye. The mean change from baseline in ETDRS letters will be presented for, both, the Treated Eye and the Control Eye groups.
At each time point, the change from baseline and the percentage change from baseline in the area of autofluoresence will be computed for each eye and their mean will be presented for, both, the Treated Eye and the Control Eye groups.
With regards to microperimetry, at each time point, the change from baseline in mean sensitivity will be computed for each eye. The mean change from baseline in mean sensitivity will be presented for, both, the Treated Eye and the Control Eye groups.

Adverse events will be listed.
Other Investigator Sponsored Studies are expected to be run with a similar protocol. A meta-analysis on the Investigator Sponsored studies is planned. A separate Statistical Analysis Plan describing the details of the meta-analysis will be developed.

18 Summary/Conclusions

18.1 Efficacy Results

Visual Acuity

The mean (SD) final BCVA ETDRS score of the treated eyes was 64.0 (0.4) (20/50 Snellen equivalent), and the control eyes scored a mean of 69.3 (0.5) letters (20/40 Snellen equivalent). The treated eyes gained a mean of 4.7 (10.9) letters at month 3 and maintained a gain of 3.7 (7.5) letters at month 24. The control eyes showed no mean change from baseline at month 24 (mean [SD], 0.0 [5.1] letters). The difference between BCVA change in the groups was 3.7 letters (95% CI, −7.2 to 14.5 letters; P = .43). At month 24, 2 patients (33%) gained 10 or more letters and 1 patient (17%) gained 15 or more letters in the treated eyes, but no such change was observed in the control eyes (difference, 33%; 95% CI, −21% to 71%; P = .50). Patients with moderate VA loss (letter score of 73-34 [approximate Snellen equivalent 20/32 to 20/200]); n = 4) in the treated eye at baseline appeared to experience larger gains in VA (mean, 5.5 letters; range, −1 to 15) than patients with better VA letter score at baseline (>73 [approximate Snellen equivalent 20/32]; loss of 2 and 3 letters). No patient in either group lost 10 or more letters when baseline values were compared with month 24 values.

Retinal sensitivity increased by 10.3 (5.5) dB in the treated eyes and 9.7 (4.9) dB in the control eyes (difference, 0.6; 95% CI, −10.2 to 11.4; P = .74). Although 5 of the 6 treated eyes achieved improvements in all or some measures (mean retinal sensitivity, peak retinal sensitivity, and/or gaze fixation area), patient 401 experienced no improvement. He developed a macular hole due to the surgery, which closed spontaneously by the end of the study. Quantitative analysis was performed on the complete cohort after excluding patient 401 to highlight the potential efficacy in a scenario without surgical complications.

Taken together, in this phase 2, open-label randomized clinical trial of 6 patients, no statistically significant differences between treated and control eyes were identified for mean change in best-corrected visual acuity or retinal sensitivity.

18.2 Safety Results

Throughout the study period, a total of 28 adverse events were reported; none of them were regarded as severe. Fifteen adverse events were ocular, mostly common symptoms following vitreoretinal surgery with sutured sclerotomies (eg, conjunctival hyperemia, foreign body sensation). Five adverse events were unresolved at the last visit: patient 401 reported worsening diplopia over the 2 years (likely due to progressive loss of an adequate visual field to fuse)15; a preexisting cataract in patient 405 worsened following vitrectomy in the treated eye; 3 patients (401, 403, and 405) developed localized idiopathic thickening of the inner retina. No plausible

relationship to the study procedure and/or study drug was documented for any of the nonocular adverse events.
For safety results please see also Appendix 1.

18.3 Conclusion

The results and data from this study show the potential of AAV-mediated gene therapy for CHM. Our study further adds to the evidence that gene therapy with AAV2-REP1 may be well tolerated, although no differences in VA from control eyes were identified in the 6 participants. The phase 3 STAR trial (NCT03496012) may help to assess more confidently the safety and efficacy of treatment with AAV2-REP1 in patients with CHM.

19 Appendices

Appendix 1: THOR Safetyreport AEs_2017_08_11