Name of Sponsor/Company: Oxurion NV	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: THR-687		
Name of Active Ingredient: THR-687		

Title of Study:

A Phase 2, randomised, multicentre study to assess the dose level of multiple THR-687 injections and to evaluate the efficacy and safety of THR-687 *versus* aflibercept for the treatment of diabetic macular oedema (DME)

Early Termination of the Study:

Study THR-687-002 was designed as a 2-part study. **Part A** of the study was conducted to select the THR-687 dose level to be compared to aflibercept in **Part B**. After all subjects in **Part A** completed the Month 3 visit, a benefit-risk assessment was performed by the Oxurion Steering Committee with the purpose to select the THR-687 dose level to be further assessed in **Part B** of the study. While the data that were reviewed by the Steering Committee showed THR-687 to be safe and well-tolerated, there was insufficient evidence of efficacy on the key outcome measures, *i.e.* best-corrected visual acuity (BCVA) and central subfield thickness (CST), at either dose level. The Steering Committee therefore decided not to advance the study to **Part B**. The subjects in **Part A** were continued to be followed up as per protocol. The abbreviated clinical study report therefore reports data of the completed **Part A** of the study.

Study Centres:

Part A of the study was conducted in study centres located in the US.

Publications (Reference):

Results of this study were not published at the time of the writing of this summary.

Studied Period (Years):	**Phase of Development:**
Date first subject enrolled in **Part A**: 27-Aug-2021 Decision of early termination (decision not to advance the study to **Part B**): 09-May-2022 Date last subject completed **Part A**: 29-Jun-2022	Phase 2

Objectives:

Primary:

The primary objective of **Part A** of the study was to select the THR-687 dose level (1.2mg or 2.0mg) to be further assessed in **Part B**.

Secondary:

- To assess the efficacy of multiple intravitreal (IVT) injections of THR-687 over-time
- To assess the safety of multiple IVT injections of THR-687 over-time

Methodology:

Part A was the randomised, dose-selection part of the study assessing 2 dose levels of THR-687.

Approximately 12 subjects were planned to be randomised (1:1 allocation) to:

- **THR-687 1.2mg.** Approximately 6 subjects were planned to receive IVT THR-687 1.2mg at Day 1, Month 1 and Month 2.
- **THR-687 2.0mg.** Approximately 6 subjects were planned to receive IVT THR-687 2.0mg at Day 1, Month 1 and Month 2.

Part A was conducted in a single-masked manner. In addition, to ensure objective assessment:

- Masked BCVA assessor(s) were assigned at each site to perform BCVA assessments.
- The central reading centre (CRC) in charge of the grading of the ophthalmic images and the laboratory in charge of the protocol-related laboratory assessments were masked to investigational medicinal product (IMP) assignment.

Number of Subjects (Planned and Analysed):

- Planned: approximately 12 subjects
- Randomised: 16 subjects: 7 to THR-687 1.2mg and 9 to THR-687 2.0mg
- All Treated Set: 16 subjects: 7 in the THR-687 1.2mg and 9 in the THR-687 2.0mg arm
- Per Protocol Set: 14 subjects: 5 in the THR-687 1.2mg and 9 in the THR-687 2.0mg arm

Diagnosis and Main Criteria for Inclusion:

Male or female adult subjects with treatment-naïve central-involved DME. Subjects could have only 1 eye treated as part of this study and had to provide written informed consent to be eligible for study participation.

The main inclusion criteria in **Part A** were:

- Type 1 or type 2 diabetes
- BCVA ETDRS letter score ≤ 78 (*i.e.* Snellen equivalent 20/32 or worse) and ≥ 39 (*i.e.* Snellen equivalent 20/160 or better) in the study eye
- Central-involved DME with CST ≥ 300µm in men, or ≥ 285µm in women, measured from the retinal pigment epithelium to the internal limiting membrane inclusively, on spectral domain optical coherence tomography (SD-OCT), in the study eye, as assessed by the CRC
- Treatment-naïve study eye with known diagnosis of DME ≤ 12 months prior to screening procedures

Test product, Dose Level and Mode of Administration:

- Test product: THR-687
- Dose levels: 1.2mg and 2.0mg
- Mode of administration: IVT injection

Duration of Treatment:

Each subject in **Part A** was planned to receive 3 IVT injections, at Day 1, Month 1 and Month 2, *i.e.* the total treatment duration was 2 months.

Reference Therapy, Dose Level and Mode of Administration:

Not applicable for **Part A** of the study.

Criteria for Evaluation:

Key Endpoints to Assess Benefit-Risk:

- Incidence of ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs)
- Development of severe intraocular inflammation: ≥ 2+ inflammation on any of the intraocular inflammation grading scales (grading of anterior chamber cells, grading of anterior chamber flare, Nussenblatt chart for vitreous inflammation grading)
- Incidence of BCVA decrease of ≥ 10 ETDRS letter score from Baseline, by study visit
- Change from Baseline in BCVA ETDRS letter score, by study visit
- Change from Baseline in CST, based on SD-OCT, as assessed by the CRC, by study visit

SAFETY SUMMARY

No SAEs were reported. There were no AEs that led to withdrawal from repeat injection, or to discontinuation from the study. There was no intraocular inflammation (AEs of Special Interest or development of severe intraocular inflammation).

Overall, from Day 1 up to EOS, 6 AEs were reported for 4/7 subjects in the THR-687 1.2mg arm, and 18 AEs were reported for 6/9 subjects in the THR-687 2.0mg arm. This included:

- One (1) AE in the study eye in the THR-687 1.2mg arm and 11 AEs in the study eye for 6/9 subjects in the THR-687 2.0mg arm.
- One (1) AE in the non-study eye in a subject in the THR-687 2.0mg arm.
- Five (5) non-ocular AEs for 3/7 subjects in the THR-687 1.2mg arm and 6 non-ocular AEs for 4/9 subjects in the THR-687 2.0mg arm.

The most frequently reported AEs in the study eye were Visual Acuity Reduced (4 AEs in total: 1 in the THR-687 1.2mg arm and 3 in the THR-687 2.0mg arm) and Retinal Thickening (3 AEs in total, all in the THR-687 2.0mg arm).

The most frequently reported non-ocular AE was Hypertension (3 AEs in total: 1 in the THR-687 1.2mg arm and 2 in the THR-687 2.0mg arm). All other non-ocular AEs had a single occurrence only.

No safety signals were observed following the review of all data obtained from the safety assessments performed in the study (including full ophthalmic examinations, BCVA assessments and HbA1c assessments).

In conclusion, 3 monthly IVT injections with THR-687 1.2mg or THR-687 2.0mg were safe and well-tolerated.