DOCUMENT TYPE	Study Protocol
PROTOCOL TITLE:	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)
PROTOCOL NUMBER:	THR-687-002
CLINICALTRIALS.GOV IDENTIFIER:	NCT05063734
PROTOCOL VERSION:	Version 2.0
PROTOCOL DATE	07-Sep-2021

CLARIFICATION NOTE

Study THR-687-002 was designed as a 2-part study. **Part A** was the randomised, dose-selection part of the study assessing 2 dose levels of THR-687. The objective of **Part A** of the study was to select the THR-687 dose level to be compared to aflibercept in **Part B**, which was the randomised, active-controlled part of the study.

THR-687 dose level selection was to be based on a benefit-risk assessment conducted by the Oxurion Steering Committee, when all subjects in **Part A** completed the Month 3 visit. However, while the benefit-risk assessment showed that THR-687 was safe and well-tolerated at all dose levels tested, there was insufficient evidence of efficacy on the key outcome measures (Best-Corrected Visual Acuity and Central Subfield Thickness). The study was therefore not advanced to **Part B**.

TITLE PAGE

Protocol Title:

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)

Short Title:

A study to evaluate THR-687 treatment for diabetic macular oedema

Protocol Number:

THR-687-002

Acronym:

INTEGRAL

Protocol Version History:

Version 1.0: 02-Apr-2021

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Compound:

THR-687

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Phase 2

Sponsor Name:

Oxurion NV

Legal Registered Address:

Gaston Geenslaan 1

B-3001 Leuven

Belgium

Regulatory Agency Identifier Numbers:

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SPONSOR SIGNATURE PAGE

PROTOCOL VERSION AND DATE: Version 2.0 (Amendment 1): 07-Sep-2021

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)

Sponsor Signatory:

[redacted] Date

[redacted]

Medical Monitor Name and Contact Information can be found in the study-specific manual.

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1.1. Synopsis

1.1.1. Protocol Title

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)

1.1.2. Brief Title

A study to evaluate THR-687 treatment for diabetic macular oedema

1.1.3. Study Rationale

Study THR-687-002 is the first study in which multiple intravitreal (IVT) injections of THR-687 will be administered in humans. The study is composed of 2 parts (also refer to the study scheme):

- **Part A** is conducted to select the THR-687 dose level to be assessed in **Part B**.
- **Part B** is conducted to evaluate the efficacy and safety of the selected THR-687 dose level from **Part A**, compared to aflibercept.

1.1.4. Study Population

Subjects with central-involved DME (CI-DME):

- **Part A** will be conducted in subjects who are treatment-naïve for DME in the study eye (*i.e.* eyes that have not been treated with anti-VEGFs, intravitreal corticosteroids, or any investigational product for DME) (further referred to as 'Rx naïve subjects').
- **Part B** will be conducted both in Rx naïve subjects, and in subjects who received prior treatment for DME in the study eye (further referred to as 'previously treated subjects').

1.1.5. Objectives

Part A

Primary Objective

The primary objective of this part of the study is to select the THR-687 dose level (1.2mg or 2.0mg) to be further assessed in **Part B**. Dose level selection will be based on a benefit-risk assessment conducted when all subjects completed the Month 3 visit.

Refer to the Key Endpoints to Assess Benefit-Risk for the related endpoints.

Other Objectives

The other objectives of this part of the study are the same as those defined for **Part B**.

Part B

Primary Objective

The primary objective of this part of the study is to assess the difference in treatment effect between THR-687 and aflibercept, in terms of the change from Baseline in best-corrected visual acuity (BCVA) at Month 3, in Rx naïve subjects.

Refer to the Primary Endpoint and Main Estimand for the related endpoint and the main estimand.

Other Objectives

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

Refer to the Secondary and the Exploratory Endpoints for the related endpoints.

1.1.6. Endpoints and Main Estimand for the Primary Endpoint

Part A

[redacted]

Part B

Primary Endpoint and Main Estimand; Rx Naïve Subjects

- The primary endpoint is defined as the change from Baseline in BCVA ETDRS letter score, at Month 3

  [redacted]

[redacted]

Secondary Endpoints

- Weighted average of the change from Baseline in BCVA ETDRS letter score from Day 8 through Month 3 using the trapezoidal rule (area under the curve [AUC])
- 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
- Incidence of ocular and non-ocular AEs and SAEs, from first injection up to the end of the study

[redacted]

[redacted]

1.1.7. Overall Design

This is a Phase 2, multicentre study composed of 2 parts (also refer to the study scheme):

- **Part A** is the randomised, single-masked, dose-selection part of the study assessing 2 dose levels of THR-687.
- **Part B** is the randomised, double-masked, active-controlled part of the study with a single dose level of THR-687 (selected from **Part A**) and aflibercept as comparator. Randomisation in **Part B** will only be initiated after dose level selection by the Steering Committee, which will be based on a benefit-risk assessment conducted when all subjects in **Part A** have completed the Month 3 visit.

1.1.8. Number of Subjects (Planned)

Part A

It is planned to randomise approximately12 subjects (approximately 6 subjects per dose level).

Part B

It is planned to randomise approximately 291 subjects in total[redacted]

- [redacted]

1.1.9. Study Treatment Arms

Part A

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

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

Part B

[redacted] Rx naïve subjects are planned to be randomised (2:1 allocation), stratified by study eye CST (as assessed by the CRC) at Screening and by study eye BCVA at Day 1, to:

- **THR-687 (selected dose level from Part A).** [redacted] subjects are planned to receive IVT THR-687 (selected dose level from **Part A**) at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with the same dose level of THR-687 at Month 3, or Month 4, or Month 5, if any of the pro re nata (PRN) criteria are met.
- **Aflibercept 2mg.** [redacted] subjects are planned to receive IVT aflibercept 2mg at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with aflibercept 2mg at Month 3, or Month 4, or Month 5, if any of PRN criteria are met.

[redacted] previously treated subjects are planned to be randomised (1:1 allocation), stratified by study eye BCVA at Day 1, to:

- **THR-687 (selected dose level from Part A).** [redacted] subjects are planned to receive IVT THR-687 (selected dose level from **Part A**) at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with the same dose level of THR-687 at Month 3, or Month 4, or Month 5, if any of the PRN criteria are met.
- **Aflibercept 2mg.** [redacted] subjects are planned to receive IVT aflibercept 2mg at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with aflibercept 2mg at Month 3, or Month 4, or Month 5, if any of PRN criteria are met.

1.1.10. Investigational Medicinal Product Allocation

Part A

Eligible subjects will be randomised to receive either THR-687 2.0mg or THR-687 1.2mg (1:1 allocation), using an interactive web response system (IWRS).

Part B

Eligible Rx naïve subjects will be randomised to receive either THR-687 (selected dose level from **Part A**) or aflibercept 2mg (2:1 allocation), using an IWRS. Randomisation will be stratified by:

- Study eye CST at Screening [redacted], **and**
- Study eye BCVA at Day 1 [redacted].

Eligible previously treated subjects will be randomised to receive either THR-687 (selected dose level from **Part A**) or aflibercept 2mg (1:1 allocation), using an IWRS. Randomisation will be stratified by study eye BCVA at Day 1 [redacted].

1.1.11. Study Duration

Part A

For each treated subject, the study duration will be 6 months from the first injection.

Part B

For each treated subject, the study duration will be 8 months from the first injection.

1.1.12. Masking

Part A

The randomised, dose-selection part of the study will be conducted in a **single-masked manner**.

In addition, to ensure objective assessment:

- Masked BCVA assessor(s) will be assigned at each site to perform BCVA assessments.
- The CRC in charge of the grading of the ophthalmic images and the laboratories in charge of the protocol-related laboratory assessments will be masked to IMP assignment.

Part B

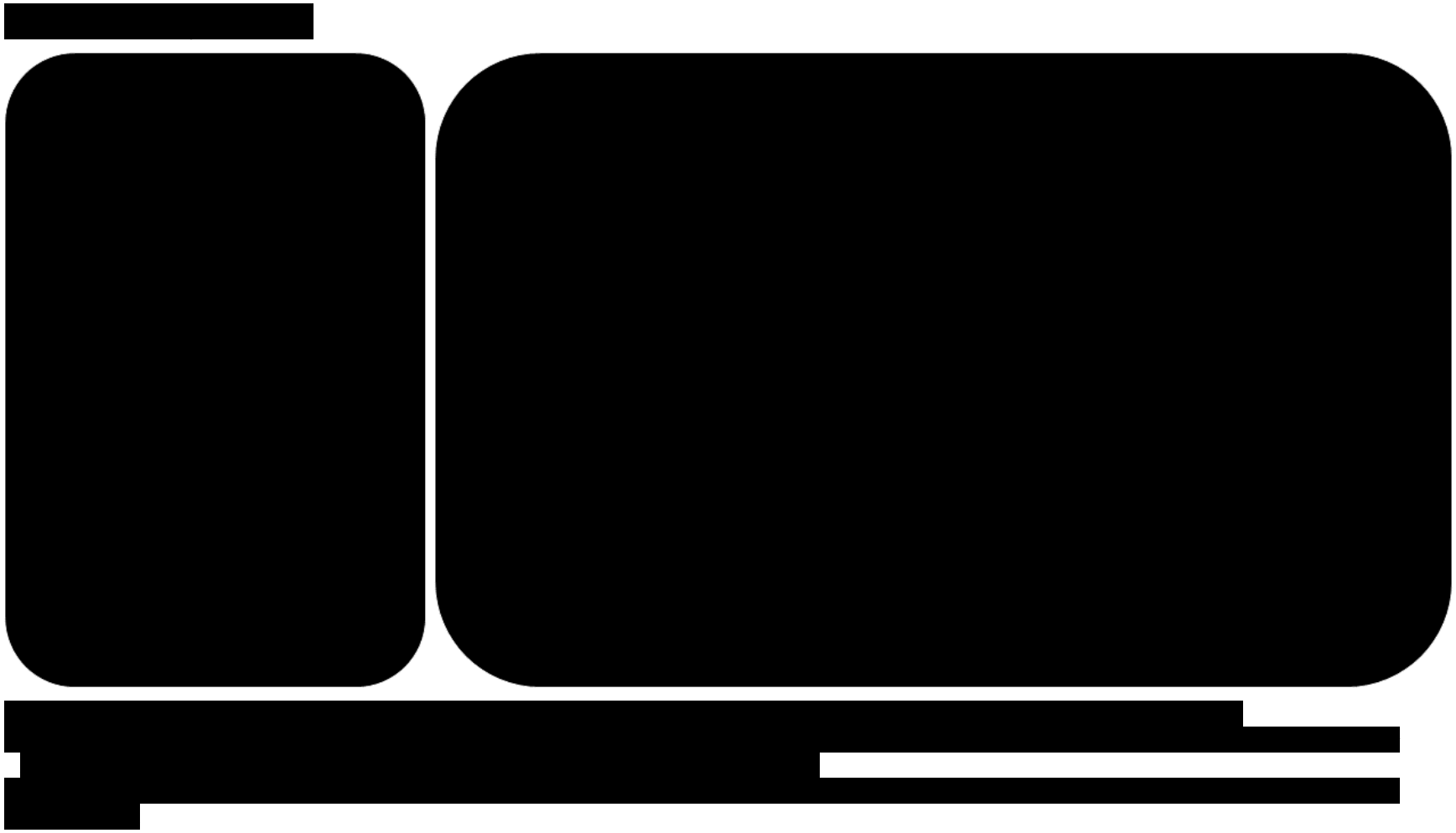
The randomised, active-controlled part of the study will be conducted in a **double-masked manner**.

In order to preserve the masking, IMP handling and administration will be performed by unmasked study personnel. IMP preparation must occur outside the subject's view, and the subject should be asked to direct his / her gaze away at all times.

1.1.13. Committees

A **Safety Monitoring Committee (SMC)** will be established**,** composed of members of relevant functional areas [redacted]

A **Steering Committee** will be established to select the dose level of THR-687 that will be assessed in **Part B**. The Steering Committee will be composed of members of relevant functional areas [redacted]



1.3. Schedules of Activities

1.3.1. Schedule of Activities – Part A of the Study

Table 1: Schedule of Activities – Part A of the Study

Contact Number	**Visit 1**	**Visit 2** [a]	[redacted]	**Visit 3**	**Visit 4** [a]	**Visit 5** [a]	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 / End of Study**	**Unscheduled Visit** [c]
Timing Visit window	**Scree-ning** [d]	**Day 1** Up to 28d post-V1	[redacted]	**Day 8** ±3d	**Month 1** Day 29 ±4d	**Month 2** Day 57 ±4d	**Month 3** Day 85 ±4d	**Month 4** Day 113 ±4d	**Month 5** Day 141 ±4d	**Month 6** Day 169 ±4d	*Any time during the study*
Assessment											
Informed consent	X										
Demography [e], medical and ocular history	X (1)										
Prior and concomitant medications and interventions	X (2)	X		X	X	X	X	X	X	X	X
Pregnancy test [f]	X (3)	X			X	X	X	X	X		
Blood pressure measurement	X (4)	X									
Ophthalmic assessments:											
BCVA (ETDRS letter score)	X [g] (5)	X		X	X	X	X	X	X	X	X
Full ophthalmic examination [h]	X [g] (6)	X		X	X	X	X	X	X	X	X
SD-OCT	X [g] (7)	X		X	X	X	X	X	X	X	X
Colour fundus photography	X [g] (8)						X			X	
Fluorescein angiography	X [g] (9)						X				
OCTA [i]	X [g]						X			X	
Biological samples:											
Blood sampling for HbA1c (~2 mL) [j]	X (10)						X			X	
[redacted]		X [l]	X								

Contact Number	**Visit 1**	**Visit 2** [a]	[redacted]	**Visit 3**	**Visit 4** [a]	**Visit 5** [a]	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 / End of Study**	**Unscheduled Visit** [c]
Timing Visit window	**Scree-ning** [d]	**Day 1** Up to 28d post-V1	[redacted]	**Day 8** ±3d	**Month 1** Day 29 ±4d	**Month 2** Day 57 ±4d	**Month 3** Day 85 ±4d	**Month 4** Day 113 ±4d	**Month 5** Day 141 ±4d	**Month 6** Day 169 ±4d	*Any time during the study*
Assessment											
[redacted]		X					X				
IMP kit number allocation		X			X	X					
Assess list of criteria leading to withdrawal from repeat injection with IMP [n]					X	X					
IMP administration (study eye)		X			X	X					
Study eye post-injection assessment [o]		X			X	X					
AE and SAE monitoring and reporting	X	X		X	X	X	X	X	X	X	X

[a] Assessments scheduled during injection visits must be performed prior to the IMP injection, except for the study eye post-injection assessment including monitoring and recording of post-injection AEs and SAEs and post-injection concomitant medications (if applicable).

[redacted]

[c] Unscheduled visits for clinical reasons may be conducted at any time during the study as per the Investigator's clinical judgement. The assessments indicated in this table must be performed during all unscheduled visits conducted for clinical reasons. Other assessment may be performed as deemed necessary depending on the reason for the unscheduled visit.

[d] At Screening, the subject's eligibility for study participation will be determined by checking all inclusion and exclusion criteria. It is mandatory to start with the non-invasive screening assessments before performing any of the invasive screening assessments, and it is recommended to do the eligibility assessment in the numerical order as indicated between brackets in Table 1. If a subject fails one of the in- / exclusion criteria, the subject will be a screen failure and no further assessments will be done. Certain in- / exclusion criteria need to be confirmed by the CRC / the central laboratory as specified in Section 5. Only if the subject is deemed eligible based on the Investigator's assessment at Screening, must the images / blood sample(s) be provided to the CRC / the central laboratory for confirmation of eligibility.

[e] Year of birth, age, sex, ethnicity and race (race and / or ethnicity will not be collected in countries where this is not permitted by the regulatory authority / IEC / IRB).

[f] Only for women of childbearing potential. Highly sensitive urine pregnancy test at all indicated visits UNLESS a serum pregnancy test is required by local regulations or the IRB / IEC, in which case a blood sample for serum pregnancy testing (~3.5mL) will be collected at Screening and a highly sensitive urine pregnancy test will be done at the other visits.

[g] Performed in both eyes. Ophthalmic assessments without this footnote are performed in the study eye only.

[h] Full ophthalmic examination including slit lamp examination, IOP assessment and dilated fundus examination.

[i] Only at sites that have the required type of OCTA equipment.

[j] To be shipped as whole blood (no processing).

[redacted]

[n] Refer to Section 7.1 for the list of criteria for withdrawal from repeat injection with IMP.

[o] The study eye post-injection assessment will include verification of optic nerve perfusion within a few minutes after the injection, as well as an IOP assessment done within 30±15 minutes after the injection. Refer to Section 6.2.3 for more detailed information.

Light grey coloured visits indicate injection visits. The dark grey coloured visit indicates unscheduled visits.

AE = adverse event; **BCVA** = best-corrected visual acuity; **d** = days; **HbA1c** = glycated haemoglobin A; **IMP** = investigational medicinal product; **mL** = millilitre; **OCTA** = optical coherence tomography angiography; **SAE** = serious adverse event; **SD-OCT** = spectral domain optical coherence tomography

1.3.2. Schedule of Activities – Part B of the Study

Table 2: Schedule of Activities – Part B of the Study

Contact Number	**Visit 1**	**Visit 2** [a]	[redacted]	**Visit 3**	**Visit 4** [a]	**Visit 5** [a]	**Visit 6** [a]	**Visit 7** [a]	**Visit 8** [a]	**Visit 9**	**Visit 10**	**Visit 11/ End of Study**	**Un-scheduled Visit** [c]
Timing Visit window	**Scree-ning** [d]	**Day 1** Up to 28d post-V1	[redacted]	**Day 8** ±3d	**Month 1** Day 29 ±4d	**Month 2** Day 57 ±4d	**Month 3** Day 85 ±4d	**Month 4** Day 113 ±4d	**Month 5** Day 141 ±4d	**Month 6** Day 169 ±4d	**Month 7** Day 197 ±4d	**Month 8** Day 225 ±4d	*Any time during the study*
Assessment													
Informed consent	X												
Demography [e], medical and ocular history [f]	X (1)												
Prior and concomitant medications and interventions	X (2)	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test [g]	X (3)	X			X	X	X	X	X	X	X	X	
Blood pressure measurement	X (4)	X											
Ophthalmic assessments:													
BCVA (ETDRS letter score)	X [h] (5)	X		X	X	X	X	X	X	X	X	X	X
Full ophthalmic examination [i]	X [h] (6)	X		X	X	X	X	X	X	X	X	X	X
SD-OCT	X [h] (7)	X		X	X	X	X	X	X	X	X	X	X
Colour fundus photography	X [h] (8)						X			X		X	
Fluorescein angiography	X [h] (9)											X	
OCTA [j]	X [h]						X			X		X	
[redacted]		X					X					X	
Biological samples:													
Blood sampling for HbA1c (~2 mL) [l]	X (10)						X					X	

Contact Number	**Visit 1**	**Visit 2** [a]	[redacted]	**Visit 3**	**Visit 4** [a]	**Visit 5** [a]	**Visit 6** [a]	**Visit 7** [a]	**Visit 8** [a]	**Visit 9**	**Visit 10**	**Visit 11/ End of Study**	**Un-scheduled Visit** [c]
Timing Visit window	**Scree-ning** [d]	**Day 1** Up to 28d post-V1	[redacted]	**Day 8** ±3d	**Month 1** Day 29 ±4d	**Month 2** Day 57 ±4d	**Month 3** Day 85 ±4d	**Month 4** Day 113 ±4d	**Month 5** Day 141 ±4d	**Month 6** Day 169 ±4d	**Month 7** Day 197 ±4d	**Month 8** Day 225 ±4d	*Any time during the study*
Assessment													
[redacted]		X[redacted]	X										
[redacted]		X					X						
IMP kit number allocation		X			X	X	(X) [p]	(X) [p]	(X) [p]				
IMP administration (study eye) [q]		X			X	X	(X) [p]	(X) [p]	(X) [p]				
Assess PRN criteria [r]							X	(X)	(X)				
Assess list of withdrawal criteria from repeat injection with IMP [s]					X	X	(X) [p]	(X) [p]	(X) [p]				
Study eye post-injection assessment [t]		X			X	X	(X) [p]	(X) [p]	(X) [p]				
AE and SAE monitoring and reporting	X	X		X	X	X	X	X	X	X	X	X	X

[a] Assessments scheduled during injection visits must be performed prior to the IMP injection, except for the study eye post-injection assessment including monitoring and recording of post-injection AEs and SAEs and post-injection concomitant medications (if applicable).

[redacted]

[c] Unscheduled visits for clinical reasons may be conducted at any time during the study as per the Investigator's clinical judgement. The assessments indicated in this table must be performed during all unscheduled visits conducted for clinical reasons. Other assessment may be performed as deemed necessary depending on the reason for the unscheduled visit.

[d] At Screening, the subject's eligibility for study participation will be determined by checking all inclusion and exclusion criteria. It is mandatory to start with the non-invasive screening assessments before performing any of the invasive screening assessments, and it is recommended to do the eligibility assessment in the numerical order as indicated between brackets in Table 2. If a subject fails one of the in- / exclusion criteria, the subject will be a screen failure and no further assessments will be done. Certain in- / exclusion criteria need to be confirmed by the CRC / the central laboratory as specified in Section 5. Only if the subject is deemed eligible based on the Investigator's assessment at Screening, must the images / blood sample(s) be provided to the CRC / the central laboratory for confirmation of eligibility.

[e] Year of birth, age, sex, ethnicity and race (race and / or ethnicity will not be collected in countries where this is not permitted by the regulatory authority / IEC / IRB).

[f] For previously treated subjects, ocular history will include visual acuity and retinal thickness measurements done prior to study entry

[g] Only for women of childbearing potential. Highly sensitive urine pregnancy test at all indicated visits UNLESS a serum pregnancy test is required by local regulations or the IRB / IEC, in which case a blood sample for serum pregnancy testing (~3.5mL) will be collected at Screening and a highly sensitive urine pregnancy test will be done at the other visits.

[h] Performed in both eyes. Ophthalmic assessments without this footnote are performed in the study eye only.

[i] Full ophthalmic examination including slit lamp examination, IOP assessment and dilated fundus examination.

[j] Only at sites that have the required type of OCTA equipment.

[redacted]

[l] To be shipped as whole blood (no processing).

[redacted]

[p] Only if the 4th injection with IMP is administered at this visit.

[q] IMP handling and administration will be performed by an unmasked study personnel.

[r] Subjects will receive a 4th IVT injection with the IMP allocated at the time of randomisation, the first time any of the PRN criteria are met at Month 3, 4, or 5 (each subject will receive maximum 4 injections with IMP in total).

[s] Refer to Section 7.1 for the list of criteria for withdrawal from repeat injection with IMP.

[t] The study eye post-injection assessment will include verification of optic nerve perfusion within a few minutes after the injection, as well as an IOP assessment done within 30±15 minutes after the injection. Refer to Section 6.2.3 for more detailed information.

Light grey coloured visits indicate IMP injection visits. Visits with hatch pattern indicate visits at which a 4th injection with IMP will be administered the first time any of the PRN criteria are met (each subject will receive maximum 4 injections with IMP in total). The dark grey coloured visit indicates unscheduled visits.

AE = adverse event; **BCVA** = best-corrected visual acuity; **d** = days; **HbA1c** = glycated haemoglobin A; **IMP** = investigational medicinal product; **IVT** = intravitreal; **mL** = millilitre; [redacted]**OCTA** = optical coherence tomography angiography; **PRN** = pro re nata; **SAE** = serious adverse event; **SD-OCT** = spectral domain optical coherence tomography

2. INTRODUCTION

2.1. Study Rationale

THR-687 was administered for the first time in humans in the Phase 1 study THR-687-001 (ClinicalTrials.gov Identifier: NCT03666923). The subjects in this study had CI-DME with a history of response to prior anti-VEGF and / or corticosteroid treatment and remained responsive to treatment in the opinion of the Investigator. It was an open-label study with a 3+3 dose-escalation design. Subjects received a single IVT injection of one of 3 different dose levels of THR-687 and were followed up for 3 months after the injection. The study showed that a single IVT injection of THR-687 was safe and well-tolerated at all dose levels tested. In addition, preliminary efficacy in terms of BCVA gain from Baseline was observed (refer to Section 2.2.3.2 for more information). The results of the Phase 1 study support the further clinical development of THR-687 for the treatment of DME.

Study THR-687-002 is the first study in which multiple IVT injections of THR-687 will be administered in humans. The study is composed of 2 parts (also refer to the study scheme):

- **Part A** is conducted to select the THR-687 dose level to be assessed in **Part B**.
- **Part B** is conducted to evaluate the efficacy and safety of the selected THR-687 dose level from **Part A**, compared to aflibercept.

2.2. Background

2.2.1. Diabetic Macular Oedema

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus and the leading cause of blindness in working-age adults in the United States, Europe, and increasingly worldwide. A meta-analysis done on studies published between 2015 and 2018 estimated the global prevalence of DR at 27.0% of patients with diabetes (Thomas *et al.,* 2019). A higher prevalence was observed in patients with type 1 diabetes compared to those with type 2 diabetes. Regional and ethnic differences in the DR prevalence rates exist. The prevalence of DR was estimated at 20.6% of patients with diabetes in Europe, 21.9% in North America & the Caribbean, 12.5% in South East Asia (lowest prevalence rate) and 36.2% in the Western Pacific Region (highest prevalence rate). DME, which is characterised by exudation and accumulation of extracellular fluid in the macula secondary to an increase in vascular permeability, is a major cause of the vision loss associated with DR. In the same meta-analysis, the global prevalence of DME was estimated at 4.6% of patients with diabetes. Regional differences in the DME prevalence rate were also observed. The prevalence of DME was estimated at 1.2% of patients with diabetes in Europe and at 2.5% in North America & The Caribbean (lowest prevalence rates), as compared to 9.1% in the Western Pacific Region and 21.5% in Africa (highest prevalence rates) (Thomas *et al.,* 2019). The prevalence of DME is expected to rise further due to the increasing prevalence of diabetes, ageing of the population and increased life expectancy: the number of adults aged 20 – 79 years with diabetes worldwide was estimated at 463 million in 2019 and is expected to increase to 700 million by 2045 (International Diabetes Federation, 2019).

2.2.2. Current Treatment Options

Refer to Schmidt-Erfurth *et al.,* 2017 (Europe) and the Diabetic Retinopathy Preferred Practice Pattern, 2019 (United States) for guidelines on DME management.

Before the era of the anti-VEGF agents, **focal / grid laser** using small, light-intensity laser burns (50-100µm in diameter) to micro-aneurysms / diffuse area of thickening in a grid pattern has been the standard-of-care treatment for DME. Different studies demonstrated the benefit of focal / grid laser photocoagulation over no treatment in terms of the prevention of vision loss (for a review, refer to Romero-Aroca *et al.,* 2014). Complications such as loss of central vision, central scotomas and decreased colour vision have however been associated with the procedure. In addition, focal laser burns have been observed to expand over time. More recently, subthreshold micropulse laser has been developed as a treatment that avoids damaging the inner neurosensory retina, thereby reducing potential complications. There is emerging evidence to suggest that similar efficacy outcomes can be achieved with micropulse laser as compared to conventional laser (for a review, refer to Scholz, Altay and Fauser, 2017). On the other hand, while photocoagulation treatment reduces the risk of visual loss and works over a long timescale, recovery of vision is much harder to achieve with laser treatment than with anti-VEGF treatments. Therefore, the indication of focal / grid laser is now limited to the treatment of patients with non-centre-involved DME. In addition, it can be used as an adjunctive option to pharmacological therapies as deferred laser surgery treatment may ultimately decrease the need for repeated anti-VEGF injections.

Pharmacologic agents are available for the treatment of DME:

- Since the marketing approval of ranibizumab for the treatment of DME, anti-VEGF agents have become the first-line standard-of-care treatment for CI-DME. VEGF is a potent vasopermeability factor contributing to the macular thickening and visual impairment associated with DME. Anti-VEGF compounds decrease angiogenesis and vascular permeability, causing regression of neovascularisation and reduction of oedema. Several clinical studies have shown that anti-VEGF treatment is more effective than focal / grid laser treatment at decreasing CST and improving vision patients with CI-DME (for a review, refer to Bahrami *et al.*, 2016). AEs related to anti-VEGF treatment are rare and mostly related to the need for repeated IVT injections over a prolonged period of time (Boyer *et al*., 2013). Many DME patients however, up to 40%, do not adequately respond to anti-VEGF treatment in terms of BCVA and / or CST improvement (Bressler *et al.*, 2016; Bressler *et al.,* 2018 Gonzalez *et al.,* 2016; Korobelnik *et al.,* 2014).
- Inflammation plays an important role in the pathogenesis of DME. Cytokines and chemokines released by leukocytes in the blood significantly increase vascular permeability leading to more fluid build-up under the retina. Corticosteroid therapies can inhibit inflammatory mediators. Several clinical studies have shown that corticosteroids are effective in decreasing CST and improving vision in DME (Boyer *et al*., 2014; Campochiaro *et al*., 2011; Elman *et al*., 2010). While the treatment burden of corticosteroid implants is much lower than that of anti-VEGF agents, IVT corticosteroids are associated with increased risks of cataract development and elevation of intraocular pressure (IOP). Overall, the use of IVT

corticosteroids in patients with DME is therefore reserved as a second-line therapy in those who respond poorly to IVT anti-VEGF therapy and is contraindicated in patients with underlying glaucoma.

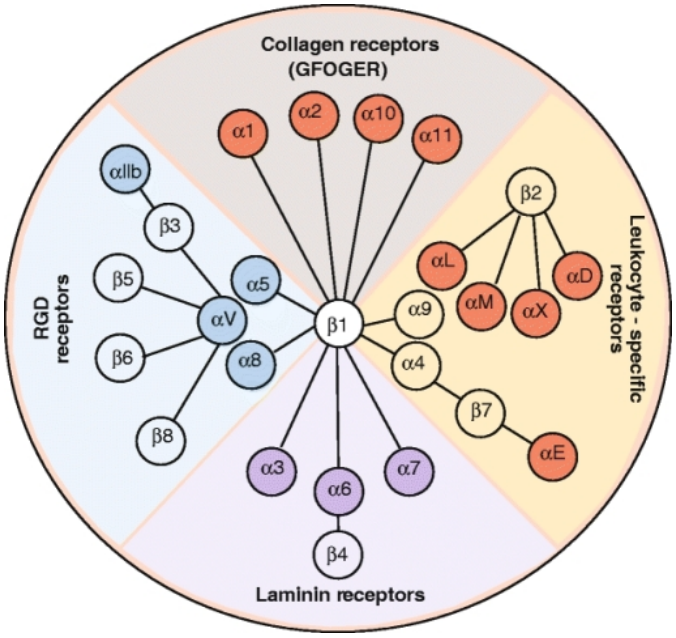
Considering that up to 40% of the patients do not adequately respond to anti-VEGF treatment (first line treatment) and the restrictions related to the available second line treatments, there is an important clinical need for additional treatments for DME.

2.2.3. THR-687

THR-687 is a small molecule directed against integrin receptors that inhibits interactions between specific integrins and their ligands. Integrins constitute a family of transmembrane cell surface receptors that can mediate cell-cell and cell-extracellular matrix interactions. Integrins play an important role in various biological processes including cell differentiation, adhesion, shape, migration, motility, invasion, proliferation, and survival. Because of their role in these biological processes, integrins also play an important role in various pathological conditions.

Integrins are obligate heterodimeric receptors consisting of a non-covalently bound α and β subunit. Different combinations of the 18 α and the 8 β known subunits constitute the family of 24 heterodimeric integrin members recognised thus far. The integrin family of receptors can be broadly classified into 4 different categories depending on their ligand recognition pattern: 1) RGD binding, 2) collagen binding, 3) laminin binding and 4) leukocyte binding types of integrins (also refer to Figure 1).

Figure 1: The Integrin Family



Taken from Barczyk, Carracedo and Gullberg, 2010

THR-687 has been shown to antagonise mainly RGD-binding integrins, including $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_5\beta_1$. These integrins have been shown to play an important role in retinal angiogenesis and vascular permeability. Interaction of integrins with the extracellular matrix can lead to neovascularisation of the retinal surface, which can eventually extend towards the vitreous

region. Immunohistological staining on human retinal tissues derived from proliferative diabetic retinopathy (PDR) patients has shown that actively proliferating vascular endothelial cells express $\alpha_v\beta_3$ and $\alpha_v\beta_5$, which are not highly expressed in quiescent endothelial cells (Friedlander *et al.*, 1996; Ning *et al.,* 2008). In addition, $\alpha_v\beta_3$ and β_3 have been shown to be expressed in fibrovascular epiretinal membranes from patients with active PDR in the fibrotic stage (Abu El-Asrar, Missotten and Geboes, 2010; Ning *et al.*, 2008), while α_5 has been shown to be overexpressed in a laser-induced mouse model of choroidal neovascularisation (CNV) (Umeda *et al.*, 2006). In line with this, several nonclinical studies have demonstrated that inhibition of integrins attenuates leukostasis and retinal vascular permeability (Iliaki *et al.*, 2009; Rao *et al.*, 2010; Santulli *et al.*, 2008). Antagonism of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ prevented retinal neovascularisation but did not harm pre-existing blood vessels (Friedlander *et al.*, 1996; Hammes *et al.*,1996; Lahdenranta *et al.*, 2007; Santulli *et al.*, 2008), while inhibition of $\alpha_5\beta_1$ inhibited endothelial cell proliferation and produce regression of choroidal neovascular membranes in different animal models (Ramakrishnan *et al.*, 2006; Umeda *et al.*, 2006).

By antagonising these integrin receptors, THR-687 is hence expected to inhibit neovascularisation and vascular leakage. Given its multifaceted mechanisms of action, THR-687 is a promising drug candidate for the treatment of retinal vascular diseases.

2.2.3.1. Nonclinical Data

The available nonclinical data support the potential of THR-687 1.2mg and THR-687 2.0mg as safe treatment options for DME. Refer to the Investigator's Brochure for a description of the available nonclinical data.

2.2.3.2. Clinical Data

The first clinical study with THR-687 (study THR-687-001) has been completed. The objective of this Phase 1 study was to evaluate the safety of a single IVT injection of 3 dose levels of THR-687. A total of 12 subjects were treated in the study: 3 subjects with THR-687 0.3mg, 3 with THR-687 0.8mg and 6 with THR-687 2.0mg.* The subjects were followed up for 3 months after the injection.

A single IVT injection with THR-687 was safe and well tolerated at all dose levels tested. No dose-limiting toxicities, SAEs or AEs leading to discontinuation from the study were reported.

Overall, 9 AEs in the study eye were reported in 5/12 (41.7%) subjects, and 4 of these AEs in 3/12 (25.0%) subjects were deemed treatment-related by the Investigator:

- The treatment-related AEs were 2 events of Conjunctival Haemorrhage (reported for 1 subject who received THR-687 0.3mg and for 1 subject who received THR-687 0.8mg), Intraocular Pressure Increased (reported for 1 subject who received THR-687 0.3mg) and Eye Pain (reported for 1 subject who received THR-687 2.0mg). All AEs that were deemed treatment-related by the Investigator were mild in severity and resolved within 28 days without treatment.
- The other (non-treatment-related) events reported in the study eye were Ocular Hypertension, Vision Blurred (1 event each) and Diabetic Retinal Oedema (3 events).

All AEs reported in the study eye were considered associated with the IVT injection procedure, underlying disease progression or concomitant diseases, and not with THR-687 itself.

While the objective of the Phase 1 study was to evaluate the safety of a single IVT injection of THR-687, preliminary efficacy in terms of BCVA gain from Baseline was observed. Overall, across study treatment arms:

- A rapid onset of action was observed: at 1, 7 and 14 days after the injection, the mean (standard deviation [SD]) gain were 3.1 (3.18), 7.2 (4.88) and 7.7 (5.16) ETDRS letters, respectively.
- The effect was the highest at 1 month after the injection, with a mean (SD) gain of 9.2 (6.38) ETDRS letters.
- The effect was maintained up to the end of the study: at Month 3, the mean (SD) gain was 8.3 (6.77) ETDRS letters.

In all study treatment arms, mean gains in BCVA from Baseline were shown at all study visits. At each visit, the largest mean gain in BCVA from Baseline was observed for the highest dose level (THR 687 2.0mg). At this dose level, the mean gains in BCVA from Baseline were 4.3, 9.8, 11.2, 10.8 and 12.5 ETDRS letters at 1 day, 7 days, 14 days, 1 month and 3 months after the injection, respectively.

Overall, across dose levels, a marginal impact on CST was observed until 1 month after the injection, with a mean (SD) decrease of -35.8 (91.89) µm at Month 1. After that, the mean CST increased to the value at Baseline, with a mean (SD) change from Baseline of +4.1 (115.63) µm at Month 3. As for BCVA, the largest effects on decrease in CST from Baseline were observed for the highest dose level (THR-687 2.0mg).

Refer to the Investigator's Brochure for a more detailed description of the available clinical data.

*

2.3. Benefit-Risk Assessment

2.3.1. Benefit Assessment

It is expected that the study treatments offer benefit to the subjects in the study:

- **THR-687:** The results of the Phase 1 study with THR-687 in previously treated subjects with CI-DME showed that a single IVT injection of THR-687 was safe and well-tolerated. In addition, mean gains in BCVA from Baseline were observed at all dose levels tested.
- **Aflibercept (Part B):** Aflibercept is an approved first-line, standard-of-care treatment for DME.
  - Most of the subjects will be naïve to treatment with aflibercept in the study eye. Per label, aflibercept treatment is to be initiated with 1 injection per month for 5 consecutive injections. Considering the treatment schedule foreseen in this study, aflibercept will not be administered per label for the majority of the subjects in the comparator arms. At the same time, it is expected that aflibercept will offer benefit in the dosing regimen used in the study. Indeed, as described in Section 4.2.4, 70 – 80% of the maximum effect of aflibercept on visual acuity improvement was observed at 1 month after the 3 first monthly injections (Korobelnik *et al.*, 2014).
  - Some of the subjects will have been previously treated with aflibercept in the study eye. This will include subjects who responded well to the treatment, and who are hence expected to benefit from continued treatment, as well as subjects who did not respond optimally to the treatment with aflibercept. It is however expected that also this latter type of subjects can benefit from the treatment with aflibercept in the study, as it has been shown that continued treatment with aflibercept in patients who do not optimally respond to the treatment, does not preclude the possibility of future development of a better response. As an example, a *post-hoc* analysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T on the 31.6% of eyes treated with aflibercept that had persistent DME (*i.e.* with CST > 250µm at each completed study visit) through 24 weeks of treatment (*i.e.* after 3 – 6 injections with aflibercept) showed that continued aflibercept treatment through 2 years resulted in long-term improvement of visual acuity (51.4% of the eyes with persistent DME at Week 24 had a gain of ≥2 lines from Baseline at Year 2), and in resolution of DME (in eyes with persistent DME at Week 24, the probability for chronic persistent DME at Year 2 was 44.2%) (Bressler *et al.,* 2018).

Another benefit of study participation is that the subjects will be closely followed up for the duration of the study, including a BCVA assessment and a full ophthalmic examination at each study visit [redacted], as well as regular ocular imaging including SD-OCT, colour fundus photography and fluorescein angiography.

An indirect benefit of study participation is that this study may contribute to the development of a new DME treatment. In addition, this study may realise overall advancement of medical and scientific knowledge that may benefit patients in the future.

2.3.2. Risk Assessment

2.3.2.1. Potential Risks Related to the Investigational Medicinal Products

Potential Risks Related to Intravitreal THR-687

This is the second clinical study in which THR-687 will be administered in humans. Given the limited human experience with THR-687, it is currently not possible to classify any AE, apart from AEs related to the IVT injection procedure, as expected.

A single IVT injection with THR-687 was safe and well-tolerated at all dose levels tested in the Phase 1 study THR-687-001. The AEs that were reported in the study eye were considered associated with the IVT injection procedure, underlying disease progression or concomitant diseases, and not with THR-687 itself (also refer to Section 2.2.3.2).

Potential Risks Related to Intravitreal Aflibercept

Refer to the Eylea® (aflibercept) label for information regarding the potential risks related to aflibercept.

2.3.2.2. Potential Risks Related to the Intravitreal Injection Procedure

The risk of complications from the IVT injection itself is low. Complications associated with IVT injections include eye pain, intraocular haemorrhage, ocular infection, transient increase in IOP, retinal detachment and floaters (Aiello *et al.*, 2004; Avery *et al.*, 2014; Charalampidou *et al.,* 2011; Jager *et al.*, 2004).

The prevalence of endophthalmitis, retinal detachment and intraocular haemorrhage after IVT injections is estimated to be 0.2%, 0.9% and 1.3% per IVT injection, respectively (Jager *et al.*, 2004). Nevertheless, careful attention to aseptic conditions, injection technique and appropriate post-injection monitoring are essential because uncommon injection-related complications may potentially lead to permanent vision loss.

2.3.2.3. Potential Risks Related to Other Study Procedures

Anaesthetic Eye Drops

Allergic reactions to anaesthetic eye drops are rare, but include itching, lid swelling and eye redness. Another risk associated with these drops is scratching of the cornea due to rubbing of the numbed eye. Study subjects must therefore be instructed not to rub their eyes until the anaesthetic wears off (about 15 minutes).

Pupil Dilation

Pupil dilation will lead to the pupils remaining dilated for several hours. This may result in light sensitivity and blurred vision (especially for near tasks). Study subjects must be told not to drive

while their pupils are dilated. Allergic reactions are rare but include eyelid swelling and eye redness.

Tonometry

If contact tonometry is used for IOP measurement, there is a small risk for corneal scratching (abrasion).

Fluorescein Angiography

Fluorescein will be injected in the systemic circulation, which may cause pain at the injection site and which carries a small risk of bleeding, bruising and / or infection at the injection site. Other side effects may include nausea, vomiting, gastrointestinal distress, headache, syncope and hypotension. In addition, the fluorescein may lead to temporary, limited darkening of the skin and urine.

In very rare cases, a severe allergic reaction can occur, which can cause breathing problems and exceptionally lead to death. For this reason, people with a history of drug reaction or allergy will be carefully monitored.

Blood Draw

Blood draw carries a small risk of pain, excessive bleeding, fainting or light-headedness, haematoma under the skin at the site of the needle insertion and a rare risk of infection.

Anterior Chamber Paracentesis

Anterior chamber paracentesis is widely performed in the management of uveitis, particularly in diagnosing infective causes. It is also commonly used to immediately lower pathological elevation of IOP. Anterior chamber paracentesis is a generally safe procedure; the incidence of complications is low when caution is exercised. Reported complications include allergy to povidone iodine, inadvertent injection of air into the anterior chamber, trauma to the cornea, iris or lens, hyphaemia, severe inflammation, infection or endophthalmitis (Azuara-Blanco and Katz, 1997; Cheung, Durrani and Murray, 2004; Helbig *et al.,* 1995; Trivedi, Denniston and Murray, 2011; Van der Lelij and Rothova, 1997). In 3 retrospective case series, a total of 361, 560 and 301 patients undergoing anterior chamber paracenteses were assessed, respectively (Kitazawa *et al.*, 2017; Trivedi, Denniston and Murray, 2011; Van der Lelij and Rothova, 1997). No long-term serious post-operative complications were reported in any of the studies. Trivedi *et al* reported 4 complications out of 560 patients (0.7%): 2 cases of inadvertent injection of air that resolved spontaneously, 1 anterior capsule touch due to sudden eye movement that was self-healing and 1 allergic reaction to povidone iodine. None of the patients reported pain (Trivedi, Denniston and Murray, 2011). Van der Lelij *et al* reported small hyphaemia in 5 out of 72 patients who were examined 30 minutes after the puncture. The depth of the anterior chamber of all evaluated patients was restored at the time of examination (Van der Lelij and Rothova, 1997).

2.3.2.4. Measures to Minimise the Risk for the Subjects in the Study

To minimise the risks for the subjects in the study, the following measures will be taken:

- For each subject, each AE will be recorded from the time of providing consent until the end of his / her participation in the study. At each study visit [redacted], the study personnel will inquire about medical complaints, and a full ophthalmic examination (including slit lamp examination, IOP assessment and dilated fundus examination) and BCVA assessment will be performed. In addition, regular ocular imaging will be performed, including SD-OCT, colour fundus photography and fluorescein angiography.
- A list of withdrawal criteria from repeat injection with IMP is provided (refer to Section 7.1). If for a subject, any of these criteria apply at the time of planned repeat injection, he / she will not receive further injection(s) with IMP but will continue study participation (apart from injection-related procedures) to ensure a complete follow-up. In addition, the Investigator may withdraw study subjects from repeat injection from IMP at his / her discretion.
- Criteria for rescue treatment are provided (refer to Section 6.7.3). When a subject who will receive no further injections with IMP experiences a worsening of DME in the study eye, rescue (standard-of-care) treatment can be administered as deemed necessary by the Investigator if one of the criteria for rescue treatment is met. These subjects will continue study participation to ensure a complete follow-up.
- As this is the first study assessing multiple IVT injections of THR-687, an SMC will be established. The SMC will be empowered to make recommendations on further study conduct. Refer to Section 9.6.1 for more information on the SMC.

2.3.3. Overall Benefit-Risk Conclusion

Considering the measures taken to minimise the risk for the subjects in the study, the Sponsor believes that the potential risks associated with study participation are justified by the anticipated benefits that may be afforded to the subjects in the study, and to patients with DME in general.

3. OBJECTIVES, ENDPOINTS AND MAIN ESTIMAND FOR THE PRIMARY ENDPOINT

3.1. Objectives

3.1.1. Part A

3.1.1.1. Primary Objective

The primary objective of this part of the study is to select the THR-687 dose level (1.2mg or 2.0mg) to be further assessed in **Part B**. Dose level selection will be based on a benefit-risk assessment conducted when all subjects completed the Month 3 visit.

Refer to Section 3.2.1.1 for the related endpoints.

3.1.1.2. Other Objectives

The other objectives of this part of the study are the same as those defined for **Part B**.

3.1.2. Part B

3.1.2.1. Primary Objective

The primary objective of this part of the study is to assess the difference in treatment effect between THR-687 and aflibercept, in terms of the change from Baseline in BCVA at Month 3, in Rx naïve subjects.

Refer to Section 3.2.2.1 for the related endpoint and the main estimand.

3.1.2.2. Other Objectives

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

Refer to Section 3.2.2.2 and to Section 3.2.2.3 for the related endpoints.

3.2. Endpoints and Main Estimand for the Primary Endpoint

3.2.1. Part A

[redacted]

[redacted]

[redacted]

[redacted]

3.2.2. Part B

3.2.2.1. Primary Endpoint and Main Estimand; Rx Naïve Subjects

- The primary endpoint is defined as the change from Baseline in BCVA ETDRS letter score, at Month 3

[redacted]

3.2.2.2. Secondary Endpoints

- Weighted average of the change from Baseline in BCVA ETDRS letter score from Day 8 through Month 3 using the trapezoidal rule (AUC)
- 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
- Incidence of ocular and non-ocular AEs and SAEs, from first injection up to the end of the study

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. STUDY DESIGN

4.1. Overall Design

- **Overall Design:** This is a Phase 2, multicentre study composed of 2 parts (also refer to the study scheme).

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

  Part B is the randomised, double-masked, active-controlled part of the study with a single dose level of THR-687 (selected from **Part A**) and aflibercept as comparator. Randomisation in **Part B** will only be initiated after dose level selection by the Steering Committee, which will be based on a benefit-risk assessment conducted when all subjects in **Part A** have completed the Month 3 visit.

- **Number of Subjects (Planned):**

  In **Part A**, it is planned to randomise approximately 12 subjects (approximately 6 subjects per dose level).

  In **Part B**, it is planned to randomise approximately 291 subjects [redacted]

  – [redacted]

- **Study Treatment Arms:**

  Part A: Approximately 12 subjects are planned to be randomised (1:1 allocation) to:

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

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

  Part B:

  [redacted] subjects are planned to be randomised (2:1 allocation), stratified by study eye CST (as assessed by the CRC) at Screening and by study eye BCVA at Day 1, to:

  – **THR-687 (selected dose level from Part A).** [redacted] subjects are planned to receive IVT THR-687 (selected dose level from **Part A**) at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with the same dose level of THR-687 at Month 3, or Month 4, or Month 5, if any of the PRN criteria are met.

– **Aflibercept 2mg.** [redacted] subjects are planned to receive IVT aflibercept 2mg at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with aflibercept 2mg at Month 3, or Month 4, or Month 5, if any of the PRN criteria are met.

[redacted] previously treated subjects are planned to be randomised (1:1 allocation), stratified by study eye BCVA at Day 1, to:

– **THR-687 (selected dose level from Part A).** [redacted] subjects are planned to receive IVT THR-687 (selected dose level from **Part A**) at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with the same dose level of THR-687 at Month 3, or Month 4, or Month 5, if any of the PRN criteria are met.

– **Aflibercept 2mg.** [redacted] subjects are planned to receive IVT aflibercept 2mg at Day 1, Month 1 and Month 2, possibly followed by a 4th injection with aflibercept 2mg at Month 3, or Month 4, or Month 5, if any of PRN criteria are met.

- **Investigational Medicinal Product Allocation:**

  Part A: Eligible subjects will be randomised to receive either THR-687 1.2mg or THR-687 2.0mg (1:1 allocation), using an IWRS.

  Part B: Eligible Rx naïve subjects will be randomised to receive either THR-687 (selected dose level from **Part A**) or aflibercept 2mg (2:1 allocation), using an IWRS. Randomisation will be stratified by:

  – Study eye CST at Screening [redacted], **and**

  – Study eye BCVA at Day 1 [redacted].

  Eligible previously treated subjects will be randomised to receive either THR-687 (selected dose level from **Part A**) or aflibercept 2mg (1:1 allocation), using an IWRS. Randomisation will be stratified by study eye BCVA at Day 1 [redacted].

- **Study Duration:**

  Part A: For each treated subject, the study duration will be 6 months from the first injection.

  Part B: For each treated subject, the study duration will be 8 months from the first injection.

- **Masking:**

  Part A: The randomised, dose-selection part of the study will be conducted in a **single-masked manner**. In addition, to ensure objective assessment:

  – Masked BCVA assessor(s) will be assigned at each site to perform BCVA assessments.

– The CRC in charge of the grading of the ophthalmic images and the laboratories in charge of the protocol-related laboratory assessments will be masked to IMP assignment.

Part B: The randomised, active-controlled part of the study will be conducted in a **double-masked manner**. In order to preserve the masking, IMP handling and administration will be performed by unmasked study personnel. IMP preparation must occur outside the subject's view, and the subject should be asked to direct his / her gaze away at all times.

- **Committees:**

  An **SMC** will be established, composed of members of relevant functional areas [redacted].

  A **Steering Committee** will be established to select the dose level of THR-687 that will be assessed in **Part B**. The Steering Committee will be composed of members of relevant functional areas [redacted].

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for the Study Population

This study will include Rx naïve subjects as well as previously treated subjects.

The main goal is to compare the treatment effect of THR-687 with that of aflibercept in eyes that are naïve to treatment for DME [redacted]. This population will allow for a direct comparison of THR-687 with an approved first-line treatment for DME (aflibercept). For that reason, all subject in **Part A** will be Rx naïve (to allow for dose level selection in this population), and the primary endpoint in **Part B** will be assessed on Rx naïve subjects only.

In addition, subjects who received prior treatment for DME in the study eye will be included in **Part B** to explore the effect of THR-687 in this population. Indeed, considering its multifaceted mechanism of action, and as supported by the Phase 1 data, THR-687 is also expected to be efficacious in this population.

[redacted]

[redacted]

4.2.3. Rationale for the Control Arm

There is no control arm in **Part A.**

Treatment with aflibercept will be used as a control in **Part B** as it is an approved standard-of-care treatment for DME.

[redacted]

[redacted]

4.3. Study Definitions

The **study start date** is the date on which the first subject signs the informed consent form (ICF).

An **enrolled subject** is any subject who provided informed consent to participate in the clinical study.

An **eligible subject** is an enrolled subject who meets all inclusion criteria and does not meet any exclusion criteria as defined in Section 5.1 and Section 5.2, respectively.

A **screen failure** is an enrolled subject who was not randomised (for any reason, *i.e.* this may be a non-eligible or an eligible subject).

A **treated subject** is a subject who received at least one injection with IMP.

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6, an **IMP** is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. The IMPs in this study are THR-687 1.2mg, THR-687 2.0mg and aflibercept.

A **withdrawal from repeat injection** is a treated subject who does not receive all injections with IMP as foreseen in the study protocol.

A treated subject will be considered **lost to follow-up** if he / she fails to return for scheduled visits and is unable to be contacted by the study site.

The **Baseline** value of an assessment is defined as the last non-missing value prior to the first administration of IMP.

Study treatment is the IMP that is planned to be administered to the subjects per the study protocol.

Rescue treatment is any standard-of-care treatment for DME (*i.e.* anti-VEGF, corticosteroid or retinal laser treatment, depending on local practice) administered in the study eye while being in the study.

The **end of the study** is the date of the last visit of the last subject in the study.

5. STUDY POPULATION

The subjects in the study will be subjects with CI-DME:

- **Part A** will be conducted in Rx naïve subjects.
- **Part B** will be conducted both in Rx naïve subjects, and in previously treated subjects.

For each subject, only 1 eye will be selected as the study eye. If both eyes are eligible, the eye with the lower BCVA will be selected as the study eye. If both eyes are eligible and have the same BCVA, the eye with the higher CST, as assessed by the CRC, will be selected as the study eye.

Refer to the study specific manual for a more detailed guidance on the selection of the study eye.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Written informed consent obtained from the subject prior to screening procedures
2. Male or female aged 18 years or older at the time of signing the informed consent
3. Type 1 or type 2 diabetes
4. BCVA ETDRS letter score [redacted] ≥ 39 (*i.e.* Snellen equivalent 20/160 or better) [redacted], in the study eye
5. CI-DME with CST ≥ 300µm in men, [redacted] measured from the retinal pigment epithelium (RPE) to the internal limiting membrane (ILM) inclusively, on SD-OCT, in the study eye, as assessed by the CRC

[redacted]

7. BCVA ETDRS letter score ≥ 34 (*i.e.* Snellen equivalent 20/200 or better) in the fellow eye

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Macular oedema due to causes other than DME in the study eye [redacted]
2. Concurrent disease in the study eye, other than DME, that could require medical or surgical intervention during the study period or could confound interpretation of the results [redacted]

3. Any condition in the study eye that could confound the ability to detect the efficacy of the IMPs [redacted]

6. [redacted]

7. Presence of iris neovascularisation in the study eye

8. Previous medications / interventions as listed below:

[redacted]

9. Planned administration of any of the medications / interventions [redacted] listed in the table above [redacted]

12. Uncontrolled glaucoma [redacted] in the study eye [redacted]

14. Previously received THR-687 or any other experimental therapy for DME, in either eye

15. Any active or suspected ocular or periocular infection, or active intraocular inflammation, in either eye [redacted]

16. Untreated diabetes [redacted]

17. Glycated haemoglobin A (HbA1c) > 12%, as assessed by the central laboratory

18. Uncontrolled hypertension [redacted]

[redacted]

5.3. Lifestyle Considerations

There are no lifestyle restrictions for study subjects before or during the study.

5.4. Screen Failures

A screen failure is an enrolled subject (*i.e.* consented to participate in the study) who does not receive any injection with IMP (for any reason, *i.e.* this may be a non-eligible or an eligible subject). A minimal set of information on screen failures is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Refer to the study-specific manual for detailed instructions on information to be recorded in the electronic case report form (eCRF) for screen failures.

For screen failures due to reasons that are expected to be temporary, one re-screening visit may be organised:

[redacted]

6. STUDY TREATMENTS AND CONCOMITANT MEDICATIONS AND INTERVENTIONS

6.1. Study Treatments

6.1.1. Considerations Related to Study Treatment Administration

At Day 1, only eligible subjects will be administered study treatment. Before each repeat injection with IMP (*i.e.* at Month 1 and Month 2 and, if applicable, before the 4th injection with IMP at Month 3, 4 or 5 [in **Part B** only]), the withdrawal criteria described in Section 7.1 will be assessed. Repeat injection with IMP will only be administered to subjects who are not withdrawn from repeat injection with IMP.

6.1.2. Part A

The study treatments that will be administered in **Part A** are presented in Table 3.

Table 3: [redacted]

[redacted]

THR-687 will be provided in **THR-687 IMP kits**, containing a THR-687 and a diluent vial, and syringes and needles (CE marked) for withdrawal, dilution (*only to be used if dilution is required*) and injection of THR-687. Refer to the study-specific manual for a detailed packaging and labelling description.

6.1.3. Part B

The study treatments that will be administered in **Part B** are presented in Table 4.

Table 4:

There will be 2 types of kits:

- **THR-687 IMP kits**, containing a THR-687 vial and a diluent vial, and syringes and needles (CE marked) for withdrawal, dilution (*only to be used if dilution is required*) and injection of THR-687.
- **Aflibercept IMP kits**, containing either a pre-filled syringe and an injection needle (CE marked); or an aflibercept vial, a syringe, and needles (CE marked) for withdrawal and injection of aflibercept.

Refer to the study-specific manual for a detailed packaging and labelling description.

6.1.3.1. PRN Criteria for 4th Injection with Investigational Medicinal Product

Subjects in **Part B** will receive a 4th injection with the allocated IMP at Month 3, Month 4, or Month 5, the first time either of the PRN criteria in Table 5 are met, as assessed by the Investigator.

Subjects will receive maximum 4 injections with IMP in total, with the last injection administered at Month 5 the latest.

[redacted]

Table 5: PRN Criteria

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

6.2. Storage, Preparation, Administration and Accountability

6.2.1. Storage

[redacted]

From a microbiological point of view, the IMPs must be used immediately after opening of the vial(s) / dilution.

6.2.2. Preparation and Administration

6.2.2.1. General Information

To maintain the masking for the study subjects, IMP preparation must occur outside the subject's view, and the subject should be asked to direct his / her gaze away at all times. In addition, in **Part B**, considering the double-masked set-up of this part of the study, IMP preparation and administration must be performed by unmasked site personnel.

The pre-injection and injection procedures, including injection tray assembly and anaesthetic preparation, will be performed under controlled aseptic conditions. This will include surgical hand disinfection, sterile gloves and disinfection of the peri-ocular skin, eyelid and ocular surface (*i.e.* cleansed with povidone iodine). Adequate anaesthesia will be administered prior to the injection as per local clinical practice. Additionally, safety measures will be implemented as required per specific institutional policies associated with IVT injections.

Only subjects enrolled in the study may receive study treatment, and only authorised site personnel may administer the injections with IMP.

6.2.2.2. Preparation and Administration

[redacted]

[redacted]

6.2.3. Study Eye Post-Injection Assessment

For each injection with IMP, a post-injection assessment must be performed within a few minutes after the injection to exclude central retinal artery non-perfusion or other complications, and can be repeated as many times as needed at the discretion of the Investigator.

The study eye must be monitored for elevated IOP within 30±15 minutes after the injection. Elevated IOP may occur in the context of the central retinal artery that remains closed for approximately 2 minutes with the subject reporting no light perception. Transient greying or obscuration of vision following injection is expected and does not need to be treated. If IOP is elevated after the injection, IOP must be monitored until the IOP decreases to normal range.

The following must be done:

1. Visualise the optic nerve head to verify reperfusion of the central retinal artery
2. Monitor IOP. Increased IOP may warrant treatment at the discretion of the Investigator (*e.g.* anterior chamber paracentesis).
3. Verify that the retina is attached and that there is no haemorrhage.

Instruct subjects that they must avoid rubbing their eye. Also instruct subjects to report any symptoms suggestive of infection, bleeding, retinal break (tear or detachment) or increased IOP without delay (*e.g.* eye pain, worsening eye redness, severely blurred or decreased vision, increased sensitivity to light, floaters).

6.2.4. Accountability

A full accountability record must be maintained by the authorised study personnel.

IMPs (both unused and used) must be stored securely. A study monitor will visit the site periodically to check inventories and ensure that the IMPs have correctly been administered and that all unused products remain intact or are quarantined. After IMP administration is completed for all subjects and upon request from the Sponsor, all IMPs must be reconciled by the study monitor. Refer to the study-specific manual for practical information on the return / destruction of used / unused IMP kits.

Under no circumstances will the IMPs be used in any manner other than directed by this protocol.

6.3. Measures to Minimise Bias: Randomisation and Masking

6.3.1. Randomisation and Investigational Medicinal Product Kit Number Allocation

In **Part A**, the target is to randomise approximately 12 subjects to THR-687 1.2mg or THR-687 2.0mg in a 1:1 allocation ratio (approximately 6 subjects per study treatment arm).
Six (6) subjects per dose level are considered to provide sufficient information to assess the benefit-risk to select a dose level of THR-687 which warrants further investigation in **Part B** (also refer to Section 9.5). Subjects in this part of the study may therefore be replaced if insufficient data are collected [redacted]

In **Part B**, the target is to randomise:

- [redacted] Rx naïve subjects to THR-687 (selected dose level from **Part A**) or aflibercept 2mg in a 2:1 allocation ratio [redacted]. Randomisation will be stratified by study eye CST at Screening [redacted] and by study eye BCVA at Day 1 [redacted].
- [redacted] previously treated subjects to THR-687 (selected dose level from **Part A**) or aflibercept 2mg in a 1:1 allocation ratio [redacted]. Randomisation will be stratified by study eye BCVA at Day 1 [redacted].

Eligible subjects will be centrally assigned to randomised study treatment using an IWRS, integrated in the eCRF. At Day 1, authorised site personnel will access the subject's eCRF to randomise the subject.

At each injection visit, IMP kit number allocation will be performed through an IWRS, integrated in the eCRF. Authorised site personnel will access the subject's eCRF to obtain the assigned IMP kit number.

Refer to the study specific manuals for practical information on randomisation and IMP kit number allocation.

6.3.2. Masking

Refer to the study specific manuals for practical information on study masking.

6.3.2.1. Part A

The randomised, dose-selection part of the study will be conducted in a **single-masked manner**. Study subjects will be masked to the IMP assignment, while all site personnel (except for the masked BCVA assessor) can be aware of the individual IMP assignment.

At the same time, to ensure objective assessment of the main study endpoints:

- Masked BCVA assessor(s) will be assigned at each site to perform BCVA assessments.
- The CRC in charge of the grading of the ophthalmic images and the laboratories in charge of the protocol-related laboratory assessments will also be masked to IMP assignment.

6.3.2.2. Part B

The randomised, active-controlled part of the study will be conducted in a **double-masked** manner. The study subjects and the site personnel will be masked to the IMP assignment. The CRC in charge of the grading of the ophthalmic images and the laboratories in charge of protocol-related laboratory assessments will also be masked to the IMP assignment.

In order to keep the masking, IMP handling and administration will be performed by unmasked study personnel. IMP preparation must occur outside the subject's view, and the subject should be asked to direct his / her gaze away at all times.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unmasked study treatment records at the site to verify that randomisation / IMP kit number allocation has been conducted accurately.

6.3.2.3. Emergency Unmasking

The IWRS (Randomisation and Trial Supply Management [RTSM] system) will be programmed with emergency unmasking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unmasking of a subject's study treatment assignment is warranted. Subject safety must always be the first consideration in making such a decision.

If the Investigator decides that emergency unmasking is warranted, the Investigator must make every effort to contact the Sponsor Medical Monitor prior to unmasking a subject's study treatment assignment, unless this could delay emergency treatment for the subject.

Refer to the study-specific manuals for practical information on emergency unmasking.

Sponsor safety personnel may unmask the study treatment assignment for any subject with a suspected unexpected serious adverse reaction (SUSAR). If the SUSAR requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's study treatment, may be sent to Investigator in accordance with local regulations.

6.4. Study Treatment Compliance

Study treatment will be administered on site by authorised, unmasked site personnel. Information on IMP preparation and administration (such as the volume used for dilution [*if applicable*], the volume injected intravitreally, as well as the date and the time of the injection), will be recorded in the subject's eCRF.

Refer to the study-specific manuals for more detailed information.

6.5. Continued Access to Study Treatment after the End of the Study

Study treatment will be provided by the Sponsor (rescue treatment will not be provided by the Sponsor).

As THR-687 is an investigational drug that has not yet been approved, it will not be available outside of the study.

Subjects should be treated as per standard-of-care after the end of the study.

6.6. Treatment of Overdose

There is no specific antidote available in case of overdosing with THR-687 or aflibercept. Treatment of overdoses will be provided based on the nature of the symptoms.

Overdosing due to increased injection volume may increase IOP. In case of overdosing due to increased injection volume, IOP must be monitored and adequate treatment will be initiated if deemed necessary.

6.7. Concomitant Medications and Interventions

All medications and interventions are allowed during the study, except those listed in Section 5.2 (in the study eye or systemically), which should ideally be avoided during the entire study period as they may confound the study results. However, if there is a worsening of DME in the study eye and the subject will receive no further injections with IMP, rescue treatment may be administered as described in Section 6.7.3.

The treatment of underlying diseases, including diabetes, is left to the subject's medical care provider.

Contact the Medical Monitor if there are any questions regarding prior or concomitant medications or interventions (ocular or non-ocular).

6.7.1. Recording of Prior and Concomitant Medications (Including Intravitreal Injections)

At Screening, the Investigator will assess prior medications taken / received by the subject (ocular and non-ocular). [redacted]

At each study contact subsequent to Screening, the Investigator will assess any medications (ocular and non-ocular) taken / received by the subject and record all in the subject's eCRF,

including anti-inflammatory and anti-infection eye drops given before or after IVT injections. Vitamins and dietary supplements will not be recorded.

6.7.2. Recording of Prior and Concomitant Interventions

At Screening, the Investigator will assess prior interventions received by the subject (ocular and non-ocular). [redacted]

At each study contact subsequent to Screening, the Investigator will assess any interventions (ocular and non-ocular) received by the subject and record all in the subject's eCRF.

6.7.3. Rescue Treatment

As per the study exclusion criteria, subjects will not be eligible for study participation if it is planned to administer any of the confounding medications / interventions as listed in Section 5.2, at any time during the study period. These medications / interventions should be avoided to be able to assess the effect of the IMP.

However, once a subject will receive no further injections with IMP (either because he /she was withdrawn from repeat injection with IMP, or because he / she received all per protocol injections with IMP), rescue treatment may be administered as deemed necessary by the Investigator if one of the criteria in Table 6 are met, as assessed by the Investigator. Once a subject received rescue treatment, he / she may hence not receive any further injections with IMP.

Rescue treatment will consist of standard-of-care treatment for DME and may hence be anti-VEGF, corticosteroid or retinal laser treatment depending on local practice. Once rescue treatment has been administered to a subject, this treatment can be continued as per standard-of-care at the discretion of the Investigator. (*i.e.* irrespective of the rescue criteria).

Table 6: Rescue Criteria

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

7. WITHDRAWAL FROM REPEAT INJECTION WITH IMP AND DISCONTINUATION FROM THE STUDY

7.1. Withdrawal from Repeat Injection with IMP

A withdrawal from repeat injection with IMP refers to any treated subject who does not receive all study treatments as foreseen in the study protocol. Once a subject is withdrawn from repeat injection with IMP, the subject will not receive further injections with IMP, however, the subject may be treated with rescue treatment, as described in Section 6.7.3.

In order to ensure a complete follow-up, subjects withdrawn from repeat injection with IMP will not be discontinued from the study and will continue all scheduled study visits and procedures, with the exception of IMP injection-related procedures (*i.e.* assessing the criteria leading to withdrawal from repeat injection with IMP, IMP kit number allocation, IMP administration and study eye post-injection assessment). The masking will be maintained for subjects who are withdrawn from repeat injection with IMP.

[redacted]

- [redacted]

Subjects may also be withdrawn from repeat injection with IMP at any time at the discretion of the Investigator (*e.g.* based on significant abnormalities on ophthalmic examination associated with the previous injection not listed in the criteria leading to withdrawal from repeat injection).

7.2. Discontinuation from the Study

A treated subject may discontinue from the study at any time at his / her own request or may be discontinued at any time at the discretion of the Investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.

- At the time of discontinuation from the study, if possible, an end of study visit should be conducted, as shown in the Schedules of Activities (SoAs).
- All data collected until the date of study discontinuation, including the data collected during the End of Study Visit, must be recorded in the subject's eCRF. The date of discontinuation from the study and the exact reason for study discontinuation will also be recorded in the subject's eCRF.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject discontinues from the study, he / she may request destruction of any samples taken and not tested. The Investigator must document this in the site study records.
- The Investigator will follow subjects who are discontinued from the study as a result of an AE or SAE until the event has resolved, stabilised, is otherwise explained, or until the subject is lost to follow-up (also refer to Section 8.3.3). If the discontinuation from the study is a result of a pregnancy, the pregnancy will need to be reported and followed-up until conclusion (also refer to Section 8.3.5).

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he / she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and / or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to re-gain contact with the subject. These contact attempts must be documented in the subject's source documents.
- Should the subject continue to be unreachable, he / she will be considered to have discontinued from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Adherence to the study design requirements is essential and required for study conduct.
- Study procedures and their timing are summarised in the SoAs. Protocol waivers or exemptions are not allowed.
- Unscheduled visits can be conducted at any time during the study. For each unscheduled visit, the reason for the visit, the visit date, the procedures performed and results obtained need to be recorded in the subject's eCRF. If an unscheduled visit is conducted for clinical reasons, as a minimum the procedures as indicated in the SoAs need to be performed. In addition, other assessment may be performed as deemed necessary depending on the reason for the unscheduled visit.
- Immediate safety concerns will be discussed with the Medical Monitor upon occurrence or awareness to determine if the subject should continue with or be withdrawn from IMP administration. Of note, if emergency unmasking is warranted and contacting the Medical Monitor could delay emergency treatment for the subject, the Investigator can proceed without contacting the Medical Monitor (refer to Section 6.3.2.3). In addition, subjects may be withdrawn from repeat injection with IMP at any time at the discretion of the Investigator (also refer to Section 7.1).
- All in- and exclusion criteria must be checked at Screening to confirm that potential subjects meet all inclusion criteria and do not meet any exclusion criteria. Standard-of-care procedures done prior to Screening cannot be used for eligibility confirmation. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable. Of note:
  - Some of the in- and exclusion criteria will need to be confirmed by the CRC / the central laboratory, as specified in Section 5.1 and Section 5.2.
  - The Investigator will re-confirm eligibility at Day 1 (by checking all criteria that can be re-confirmed by the Investigator, including blood pressure measurement, highly sensitive urine pregnancy test [for women of childbearing potential], BCVA assessment, full ophthalmic examination, recording of concomitant medications and interventions, AEs and SAEs) before randomisation.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoAs.

8.1.1. Best-Corrected Visual Acuity

BCVA will be reported as ETDRS letter score. BCVA will be assessed by a qualified BCVA assessor who will be masked to IMP assignment (refer to Section 6.3.2).

Refer to the study-specific manual for practical information on BCVA assessment.

8.1.2. Spectral Domain Optical Coherence Tomography

SD-OCT imaging will be used to assess the retina, including CST, centre point thickness, total macular volume and other parameters such as presence of intraretinal and subretinal fluid. SD-OCT imaging will be performed by a CRC-certified photographer using CRC-certified equipment. SD-OCT images will be submitted to and graded by the CRC.

Refer to the study-specific manuals for practical information on certifications, imaging procedures and submission of the images to the CRC.

8.1.3. Fluorescein Angiography

Fluorescein angiography will be used to assess retinal ischaemia and leakage. Fluorescein angiography will be performed by a CRC-certified photographer using CRC-certified equipment. Fluorescein angiographs will be submitted to and evaluated by the CRC.

Refer to the study-specific manuals for practical information on certifications, imaging procedures and submission of the images to the CRC.

8.1.4. Colour Fundus Photography

Colour fundus photography will be used to assess DR severity (ETDRS severity level). Colour fundus photography will be performed by a CRC-certified photographer using CRC-certified equipment. Colour fundus photographs will be submitted to and graded by the CRC.

Refer to the study-specific manuals for practical information on certifications, imaging procedures and submission of the images to the CRC.

8.1.5. Optical Coherence Tomography Angiography

OCTA will be used to assess vascular density and foveal avascular zone area. OCTA will be done at sites that have the required type of OCTA equipment and that are willing to do the imaging. OCTA will be performed by CRC-certified photographers using CRC-certified equipment. OCTA images will be submitted to and graded by the CRC.

Refer to the study-specific manuals for practical information on certifications, imaging procedures and submission of the images to the CRC.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoAs.

8.2.1. Full Ophthalmic Examination

Full ophthalmic examination will consist of slit lamp examination, IOP assessment and dilated fundus examination. Full ophthalmic examination will be performed by authorised site personnel.

Any clinically significant abnormalities detected during the full ophthalmic examination which are present at the time of Screening must also be recorded in the Ocular History section of the subject's eCRF (*e.g.* all subjects are expected to have a clinically significant abnormal macula in the study eye). Any new clinically significant abnormalities that arise after Screening must also be recorded in the AE section of the subject's eCRF.

8.2.2. Best-Corrected Visual Acuity

BCVA is both a measure of efficacy (gain from Baseline in ETDRS letter score) and safety (decrease from Baseline in ETDRS letter score). Refer to Section 8.1.1 for more information.

8.2.3. HbA1c

Blood samples (approximately 2mL) to asses HbA1c values will be collected. These blood samples do not require processing and will be shipped ambiently to the central laboratory for determination of the HbA1c value. The reports received from the central laboratory must be filed with the source documents.

Refer to the study-specific manual for more information on blood sampling, storage, shipment and result availability.

The Investigator must review the central laboratory report, document his / her review, and record any clinically relevant changes that are more severe than expected for the subject's condition in the AE section of the subject's eCRF (also refer to Appendix 3). The Investigator will refer the subject to his / her medical care provider if treatment is deemed required.

8.2.4. Pregnancy Testing

Pregnancy testing for women of childbearing potential will be done locally by using the provided highly sensitive urine pregnancy tests.

If serum pregnancy testing is required by local regulations or the IRB / IEC, a blood sample for pregnancy testing will be collected at Screening (approximately 3.5mL). This blood sample will be processed to serum and shipped to the central laboratory for highly sensitive serum testing. At all other visits, pregnancy testing will be done locally by using the provided highly sensitive urine pregnancy tests.

Refer to Section 8.3.5 for additional information regarding pregnancy, and to the study-specific manuals for more information regarding pregnancy testing and, if applicable, blood sampling, processing and shipment for serum pregnancy testing.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events

All AEs and SAEs will be collected from the time the subject provides consent to participate in the study until the end of the study (last study visit) for the subject. Any clinically significant medical abnormalities that are present before Screening must be recorded in the Medical History or the Ocular History section of the subject's eCRF (as applicable).

All SAEs will be recorded and reported **immediately** and under no circumstance can this exceed 24 hours. SAEs will be reported by completing the SAE form in the subject's eCRF (also refer to Appendix 3). The Investigator (or his / her designee) will complete the SAE form as thoroughly as possible and verify the information with the corresponding source documents. The Investigator will submit any updated SAE data within 24 hours of it being available.

If the eCRF system does not work, the Investigator (or his / her designee) will provide the information to the Sponsor by completing the paper SAE form, which will be provided to the Sponsor by email ([redacted]) within 24 hours. This back-up system will only be used if the eCRF is not working and NOT if the system is slow. As soon as the eCRF is working again, the Investigator (or his / her designee) must complete the electronic SAE form.

Investigators are not obliged to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he / she deems the event to be reasonably related to the study treatment or to study participation, the Investigator must promptly notify the Sponsor, either by completing the SAE form in the subject's eCRF (if still possible), or by completing the paper SAE form and providing it to the Sponsor by email ([redacted]).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The Investigator will question the subject about any medical complaints (including new medical complaints and changes [worsening, improvement or disappearance] of complaints that he / she was having). Care must be taken not to introduce bias when detecting AEs and / or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. In addition, AEs or SAEs can be detected by the Investigator by performing study assessments (*e.g.* full ophthalmic examination).

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial reporting of the AE or the SAE, the Investigator is required to proactively follow up on the event as follows:

- All AEs that lead to discontinuation from the study and all SAEs will be followed up until the event has resolved, stabilised, is otherwise explained, or the subject is lost to follow-up, whichever occurs first.
- All other AEs will be followed up until the event has resolved, stabilised, is otherwise explained, the subject is lost to follow-up, or the subject has completed the study, whichever occurs first.

Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt reporting of SAEs to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of the subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs / IECs and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (*e.g.* summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB / IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5. Pregnancy

8.3.5.1. Women of Childbearing Potential

- Women of childbearing potential must agree to use a highly effective birth control method, up to the Month 5 visit for subjects in **Part A**, and up to the Month 8 visit for subjects in **Part B**. The Investigator must counsel study subjects about the possible untoward effects on the foetus. Since [redacted] studies in animals with aflibercept have shown embryo-foetal toxicity, the Investigator is required to actively follow up the subject's adherence to their birth control method.
- Women of childbearing potential will only be eligible for study participation after a negative highly sensitive pregnancy test at Screening and at Day 1. In addition, a highly sensitive pregnancy test will be taken before each repeat injection with IMP. Women who are pregnant at that time must be withdrawn from repeat injection with

IMP. These women will not be discontinued from the study and, apart from IMP injection-related procedures, will continue all scheduled study visits and procedures to ensure complete follow-up. Refer to Section 7.1 for more information on withdrawal from repeat injection with IMP.

- The Investigator will immediately (within 24 hours after receipt or awareness of the information) report pregnancies occurring in female subjects, from the time they received the first injection with IMP, up to the Month 5 visit for subjects in **Part A**, and up to the Month 8 visit for subjects in **Part B**. The Investigator will provide the information by completing the paper Pregnancy / Prenatal Exposure form, which will be provided to the Sponsor by email ([redacted]).
- Pregnancies will be monitored until conclusion. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented via the Pregnancy Follow-up form, including for subjects who discontinued from the study, or who completed the study.
- Pregnancy in itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (and not the pregnancy itself). If an adverse condition that results from pregnancy is deemed serious, an SAE form must be completed. Abnormal pregnancy outcomes (*e.g.* spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The Investigator is not obliged to actively seek information on pregnancies after conclusion of the study participation. However, if he / she learns of any post-study pregnancy-related SAE, and he / she deems the event to be reasonably related to the study treatment, the Investigator must promptly notify the Sponsor by completing the paper Pregnancy / Prenatal Exposure form and providing it to the Sponsor by email ([redacted]).

8.3.5.2. Men of Reproductive Potential

As per the study eligibility criteria (refer to Section 5.2), men of reproductive potential must use contraception (where 1 method is barrier at the minimum) up to and including the Month 5 visit (for subjects participating in **Part A**), or up to and including the Month 8 visit (for subject participating in **Part B**). In the event of unexpected pregnancy in partners from male subjects participating in the study, the pregnancy will not be followed up, unless required by the local regulatory authorities or the IRB / IEC.

[redacted]

[redacted]

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Immunogenicity Assessments

THR-687 is a small molecule that is not thought to be immunogenic. Immunogenicity assessments will therefore not be performed.

8.7. Medical Resource Utilisation and Health Economics

Health Economics / Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

[redacted]

9.1. Statistical Hypotheses

The study consists of 2 parts: a randomised, single-masked, dose-selection part (**Part A**), and a randomised, double-masked, active-controlled part (**Part B**). The THR-687 dose level selected in **Part A** will be compared to aflibercept in **Part B**. Statistical hypothesis testing only applies to Rx naïve subjects in **Part B** of the study.

[redacted]

9.1.1. Multiplicity Adjustment

[redacted]

9.2. Analysis Sets

Analysis sets will be defined for both parts of the study as presented in Table 7. For simplicity, reference to the study part is only done for **Part A**. [redacted]

Table 7: Analysis Sets

Study Part	Analysis Set	Description
Part A Randomised, single-masked, dose-selection	Enrolled in Part A	Includes all enrolled subjects.
	Randomised in Part A	Includes all enrolled subjects randomised to IMP.
	All Treated in Part A	Includes all randomised subjects in **Part A** who received at least 1 injection with IMP. Subjects will be analysed according to the first IMP they actually received.
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

9.3. Statistical Analyses

9.3.1. General Considerations

9.3.1.1. Procedure for Accounting for Missing Data

All reasonable efforts will be made to obtain complete data for all subjects. However, missing observations may occur due to subjects lost to follow-up or to noncompliance with required study visits and / or assessments. Management of dropouts and missing data will depend on their frequency and the nature of the outcome parameter.

Unless otherwise specified, missing data for efficacy related endpoints will be imputed using a multiple imputation model in case of monotone missingness, and Last Observation Carried Forward (LOCF) in case of an intermediate missing value (*i.e.* between visits). In general, no missing data will be imputed for safety related parameters.

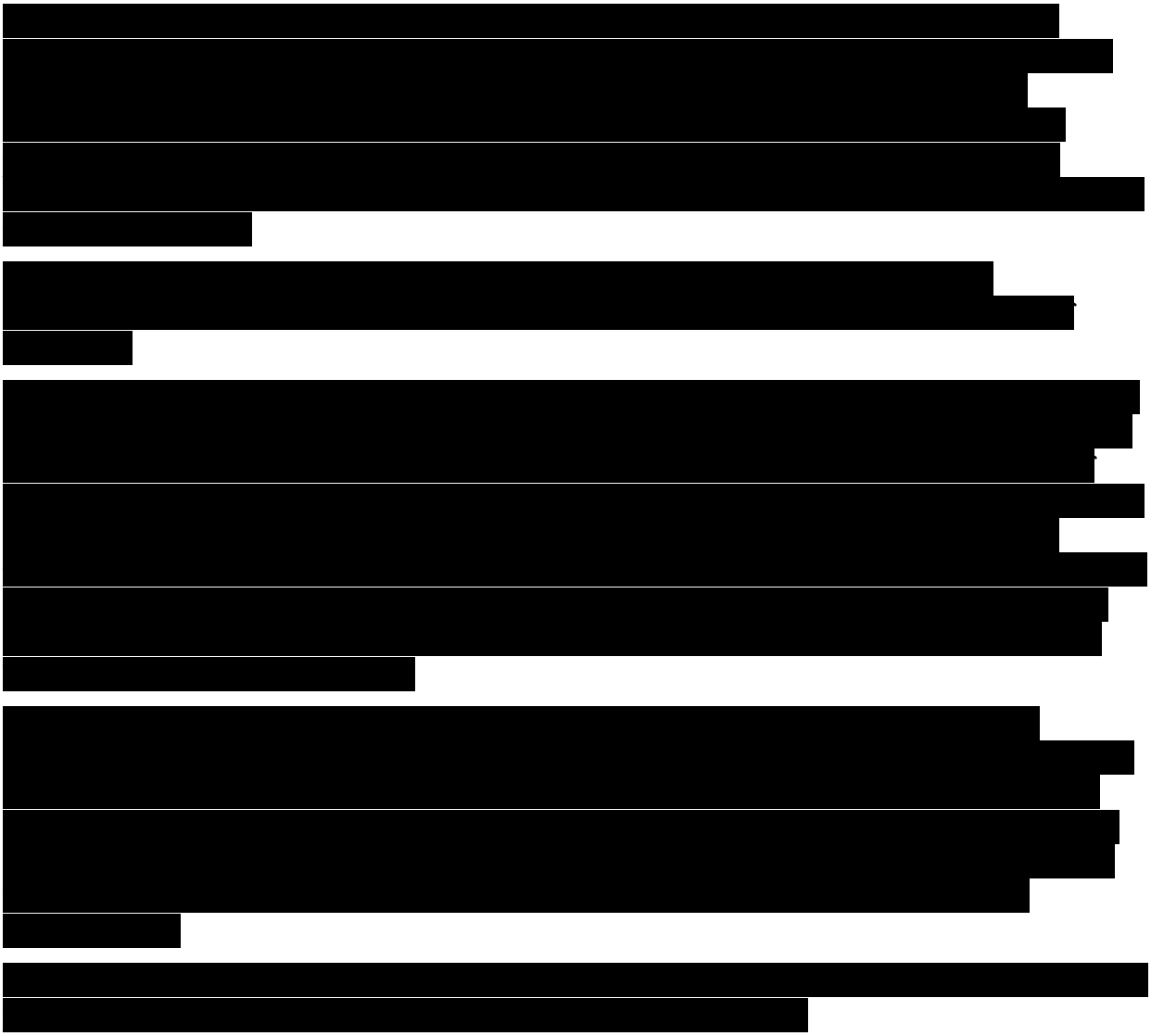
9.3.1.2. Analytical Methods Used in Part A

In **Part A**, all analyses will be performed on the All Treated analysis set. All endpoints will be analysed descriptively within each THR-687 dose level, and overall.

Summary statistics for continuous outcome measures will include number of available observations, mean, SD, standard error (SE), median, minimum, and maximum, and where applicable 95% CI for the mean. For endpoints assessed at different visits, these summaries will be presented by visit.

Categorical data, including shifts from Baseline, will be summarised by presenting count and percentage, and where applicable 95% CI for the proportion (Clopper-Pearson method).

9.3.1.3. Analytical Methods Used in Part B



9.3.2. Efficacy Analyses

9.3.2.1. Primary Endpoint and Estimand Analysis; Rx Naïve Subjects (Part B)

[redacted]

9.3.2.2. Other Endpoints Analysis

All efficacy endpoints in **Part A** will be summarised by THR-687 dose level, [redacted]

9.3.3. Safety Analyses

Safety analyses will be performed using the All Treated analysis set. The safety analyses will be summarised descriptively. In **Part A,** data will be presented within and across the dose levels. [redacted]

9.3.4. Other Analyses

[redacted]

9.4. Sequence of Analyses

The following analyses will be performed:

- An analysis supporting the benefit-risk assessment done by the Steering Committee will be conducted when all subjects in **Part A** completed the Month 3 visit
- An analysis of all data pertaining to **Part A,** when all data up to Month 6 / End of Study is available for all subjects in **Part A**
- A final analysis of the study when all data up to Month 8 / End of Study are available for all subjects in **Part B**

9.5. Sample Size Determination

The sample size in **Part A** is not based on statistical grounds. Approximately 12 subjects will be randomised to 2 different dose levels of THR-687 in a 1:1 ratio (no stratification).

Six (6) subjects per dose level are considered to provide sufficient information to assess the benefit-risk to select a dose level of THR-687 which warrants further investigation in **Part B**.

The sample size in **Part B** is determined separately in each of the subpopulations:

1. [redacted]Rx naïve subjects: [redacted] subjects will be randomly assigned to either THR-687 or aflibercept in a 2:1 ratio [redacted], stratified by study eye CST at Screening [redacted]
2. Previously treated subjects: [redacted] subjects will be randomised to either THR-687 or aflibercept in a 1:1 ratio, stratified by study eye BCVA at Day 1 [redacted]. Analyses in this subpopulation will be exploratory in nature and no formal hypothesis testing will be performed to compare study treatment arms. [redacted]

9.6. Committees

9.6.1. Safety Monitoring Committee

As this is the first study assessing multiple IVT injections of THR-687, an SMC will be established. The SMC will be composed of members of relevant functional areas [redacted]

[redacted] scheduled SMC reviews will be conducted during **Part A**:

- After [redacted] in total have received their 2nd injection with IMP and data for these subjects have been collected at least up to Month 1.
- After [redacted] in total have received their 3rd injection and data for these subjects have been collected at least up to Month 2.
- After [redacted] in total have received their 3rd injection and data for these subjects have been collected at least up to Month 2.

In addition, if there is a safety concern outside of the scheduled SMC meeting, an *ad hoc* **SMC** meeting will convene.

[redacted]

Moreover, the Investigator must alert the SMC if any event occurs, **at any time during the study**, that is deemed important enough to trigger an overall safety assessment.

The Investigator will report such events **immediately** and no later than 24 hours after receipt of awareness of the information, **by completing the SMC reporting form.** The Investigator will send the completed form by email to the SMC. Refer to the study-specific manual for practical details on reporting of these events.

Upon receipt of the information, the SMC will decide whether an *ad hoc* SMC meeting needs to be convened.

The SMC will be empowered to make recommendations on further study conduct.

The procedures that the SMC will follow during its review(s), as well as the information flow to and from the SMC, are described in the SMC Charter.

9.6.2. Steering Committee

A Steering Committee will be established, composed of members of relevant functional areas [redacted]

The Steering Committee will assess the benefit-risk of the 2 dose levels assessed in **Part A** by reviewing all available safety and efficacy data collected by the time all subjects in **Part A** have completed the Month 3 visit. The objective of this review will be to select the dose level to use in **Part B** of the study.

[redacted]

[redacted]

To determine whether a dose level is considered safe, the Steering Committee will consider whether any event that occurred is related to the IMP, and / or whether the event could be effectively treated or resolved without treatment prior to the next visit.

The assessment of **efficacy** will include the review of the following:

[redacted]

The Steering Committee will select the dose level to be further assessed in **Part B** of the study, based on the benefit-risk assessment using their clinical judgement.

[redacted]

The procedures that the Steering Committee will follow during its review, as well as the information flow to and from the Steering Committee, are described in the Steering Committee Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the study protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH Good Clinical Practice (GCP) guidelines.
  - Applicable laws and regulations.
- The Sponsor will obtain favourable opinion / approval to conduct the study from the appropriate regulatory agencies, in accordance with all local regulatory requirements.
- The protocol, protocol amendments, patient information sheet (PIS) / ICF, Investigator's Brochure and other relevant documents (*e.g.* subject recruitment materials) will be submitted to an IRB / IEC and reviewed and approved by the IRB / IEC.
- Any substantial amendments to the protocol will require regulatory agency, IRB / IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB / IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB / IEC.
  - Notifying the IRB / IEC of SAEs or other significant safety findings as required by IRB / IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB / IEC, European regulation 536/2014 and all other applicable local regulations.

10.1.2. Financial Disclosure

The Investigator and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Subjects are required to provide signed and dated informed consent prior to study participation. The authorised person obtaining the informed consent must also sign the ICF. A copy the PIS and the signed ICF will be provided to the subject.
- Before signing of the ICF, the Investigator or his / her authorised representative will explain the nature, purpose, risks and benefits of the study to the subject, and answer all questions he / she has regarding the study. Subjects must be allowed sufficient time to consider the information provided.
- Subjects must be informed that their participation is voluntary and that they are free to discontinue their participation in the study at any time.
- The PIS / ICF will meet the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and those from the IRB / IEC or study site.
- A statement that written information consent was obtained prior to study participation, as well as the date the consent was obtained, must be included in the subject's medical records.
- Whenever applicable, subjects must be re-consented to the most current version of the PIS / ICF during their participation in the study.

10.1.4. Data Protection

- At each site, a unique identifier (subject number) will be assigned to subjects who have consented to participate in the study. Any subject records or datasets that are transferred to the Sponsor will contain the subject number only; the name of the subject or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his / her coded study-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject, who will be required to give consent for his / her data to be used as described in the PIS.
- The subject must be informed that his / her medical records may be examined at the study site by Clinical Quality Assurance auditors, other authorised personnel from the

Sponsor or a delegate, IRB / IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

At the conclusion of the study, after the data are analysed, a clinical study report will be prepared.

Summaries of the results of the study will be posted on publicly available clinical trial registries as required.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded in the eCRFs unless transmitted to the Sponsor or designee electronically (*e.g.* laboratory data). Refer to the study-specific manual for guidance on completion of the eCRF.
- The Investigator is responsible for verifying that eCRF data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes, methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring methods (central, remote, or on-site monitoring) will be described in the monitoring plan.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact subject safety and / or reliability of study results. These pre-defined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (such as the contract research organisation [CRO] working on behalf of the Sponsor).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in a safe and secure location for at least 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- The Investigator must maintain accurate documentation (source documents) that supports the information recorded in the eCRF.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data recorded in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Study monitors from the CRO will perform ongoing source data verification to confirm that data recorded into the eCRF are accurate, complete, and verifiable from source documents; that the safety and rights of the subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study / Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs / IRBs and the regulatory authorities of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects and will assure appropriate subject therapy and / or follow-up.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further THR-687 development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB / IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator.
- Total number of subjects included earlier than expected.

A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

10.2. Appendix 2: Clinical Laboratory Tests

Samples will not be labelled with information that directly identifies the subject but will be coded with the subject number assigned in this study.

The Investigator cannot use the samples for any other purpose than what is described in the study protocol or its amendment(s).

Table 8: Protocol-Required Laboratory Tests

System	Test	Component	Method	Testing Laboratory
Urine	Pregnancy	Human chorionic gonadotropin	Commercial, highly sensitive urine pregnancy test provided by the central laboratory	Local (site)
Serum [a]	Pregnancy	Human chorionic gonadotropin	Commercial	Central laboratory
Whole blood	Haematology	HbA1c	Commercial	Central laboratory

[a] Only if a serum pregnancy test is required by local regulations or the IRB / IEC.
HbA1c = glycated haemoglobin A

The Investigator must document their review of each laboratory safety report.

Table 9: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of an Adverse Event

AE Definition (ICH Guideline E2A Definition)

- An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
- An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry or urinalysis) or other safety assessments (*e.g.* electrocardiogram, radiological scans, vital signs measurements), including those that worsen from Baseline, deemed clinically significant in the medical and scientific judgment of the Investigator (*i.e.* not associated with the subject's underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and / or severity of the condition.
- New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the IMP or a concomitant medication. Overdose per se will not be reported as an AE / SAE unless it is an intentional overdose taken with possible suicidal / self-harming intent. Such overdoses must be reported regardless of sequelae.
- Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE will be considered serious.

Lack of efficacy per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and / or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, **unless** judged by the Investigator to be more severe than expected for the subject's condition.
- The disease / disorder being studied or expected progression, signs, or symptoms of the disease / disorder being studied, **unless** more severe than expected for the subject's condition.

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Medical or surgical procedures (*e.g.* endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and / or convenience admission to a hospital).
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from Baseline.

10.3.2. Definition of a Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (*e.g.* hospitalisation for signs / symptoms of the disease under study).

SAE Definition (ICH guideline E2A definition)

An SAE is defined as any untoward medical occurrence that, at any dose level:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and / or treatment that would not have been appropriate in the physician's office or outpatient setting.

d. Results in persistent disability / incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (*e.g.* sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

a. Is a congenital anomaly / birth defect

b. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events will also usually be considered serious.
- Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

10.3.3. Recording, Assessment and Follow-Up of Adverse Events and Serious Adverse Events

AE and SAE Recording

- When an AE / SAE occurs, it is the responsibility of the Investigator to review all documentation (*e.g.* hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE / SAE information in the subject's eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE / SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or the delegated Pharmacovigilance Service Provider. In this case, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and / or other clinical information. Whenever possible, the diagnosis (not the individual signs / symptoms) will be documented as the AE / SAE.

Assessment of Severity

The Investigator will assess severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

An AE that is assessed as severe must not be confused with a SAE. Severe is a category utilised for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. A severe AE can be of relatively minor medical significance / non-serious (*e.g.* severe itching). Similarly, an SAE can be of mild severity (*e.g.* mild chest pain).

Assessment of Causality

- For each AE / SAE, the Investigator is obligated to assess whether there is a reasonable possibility that the event is related to:
  - The IMP
  - The IVT injection procedure
  - Any other study procedure (apart from IMP administration)

  The Investigator will use clinical judgement to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and / or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The investigator will also consult the THR-687 Investigator's Brochure and the aflibercept label in his / her assessment.
- For each AE / SAE, the Investigator **must** document in the medical notes that he / she has reviewed the AE / SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial SAE report to the Sponsor. However, it is very important that the assessment of causality is made at the time of the initial SAE report because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his/her opinion on relationship to IMP in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and / or evaluations as medically indicated or as requested by the Sponsor or the delegated Pharmacovigilance Service Provider to elucidate the nature and / or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Treatment of any AE or SAE is at the sole discretion of the Investigator and according to current good medical practice. The treatment / procedure will be recorded in the subject's eCRF.
- If a subject dies during participation in the study, the Investigator will provide a copy of any post-mortem findings including histopathology.
- New or updated information on AEs or SAEs will be recorded in the originally completed eCRF. For SAEs, which need to be followed up until the event has resolved, stabilised, is otherwise explained, or the subject is lost to follow-up, if the eCRF has been locked at the time of receiving the new or updated information, the updated information will be provided by completing the paper SAE form and providing it to the Sponsor by email ([redacted]).
- The Investigator will submit any updated SAE data within 24 hours of it being available.

10.3.4. Reporting of Serious Adverse Events

SAE Reporting via the eCRF

- The primary mechanism for reporting of SAEs will be the subject's eCRF.
- If the electronic system is unavailable, the site will use the paper SAE form (see next section) to report the event within 24 hours.
- As soon as the eCRF is working again, the Investigator (or his / her designee) must complete the electronic SAE form.
- After the study is completed and the source-verification and quality check of the data has been done, the database will be locked, *i.e.* the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the eCRF has been taken off-line, then the site must report this information using the paper SAE form (see next section).

SAE Reporting via the Paper SAE Form

- In rare circumstances when the eCRF system does not work, SAEs can be reported to the Sponsor by email using the paper SAE form. This back-up system will only be used if the eCRF is not working and NOT if the system is slow.
- Initial notification via the paper SAE form does not replace the need for the Investigator to complete and sign the SAE eCRF pages as soon as the eCRF is working again.
- After the eCRF has been locked, SAE reporting will be done using the paper SAE form (follow-up information of SAEs that started during the study, or the reporting of new SAEs reasonably related to the IMP, the injection procedure or to any other study procedure).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definition of Woman of Childbearing Potential

Woman of Childbearing Potential
• A woman is considered of childbearing potential*, i.e.* fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. • If fertility is unclear (*e.g.* amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed, additional evaluation should be considered.

Women in the Following Categories are <u>NOT</u> Considered Women of Childbearing Potential:
1. Premenarchal 2. Premenopausal female with 1 of the following: • Documented hysterectomy • Documented bilateral salpingectomy • Documented bilateral oophorectomy For women with permanent infertility due to an alternate medical cause other than the above (*e.g.* mullerian agenesis, androgen insensitivity), Investigator discretion will be applied to determine the need for pregnancy testing. NOTE: Documentation can come from the site personnel: review of the subject's medical records, medical examination, or medical history interview. 3. Postmenopausal female • A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. • A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

10.4.2. Definition of Highly Effective Birth Control Methods

Highly Effective Birth Control Methods
Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods include: • combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: – oral – intravaginal – transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation: – oral – injectable – implantable • intrauterine device • intrauterine hormone-releasing system • bilateral tubal occlusion • vasectomised partner (provided that partner is the sole sexual partner of the study subject and that the vasectomised partner has received medical assessment of the surgical success) • sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMPs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject)

10.4.3. Collection of Pregnancy Information

10.4.3.1. Female Subjects who Become Pregnant

Refer to Section 8.3.5.1.

10.4.3.2. Male Subjects with Partners who Become Pregnant

Refer to Section 8.3.5.2.

10.5. Appendix 5: Abbreviations

AE	Adverse Event
[redacted]	[redacted]
AUC	Area Under the Curve
BCVA	Best-Corrected Visual Acuity
°C	Degrees Celsius
CI	Confidence Interval
CI-DME	Central-Involved Diabetic Macular Oedema
CIOMS	Council for International Organizations of Medical Sciences
CNV	Choroidal Neovascularisation
CONSORT	Consolidated Standards of Reporting Trials
CRC	Central Reading Centre
CRO	Contract Research Organisation
CST	Central Subfield Thickness
D	Diopter
DME	Diabetic Macular Oedema
DR	Diabetic Retinopathy
eCRF	electronic Case Report Form
ETDRS	International Clinical Diabetic Retinopathy Disease Severity Scale
°F	Degrees Fahrenheit
[redacted]	[redacted]
FSH	Follicle Stimulating Hormone
G	Gauge
GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin A
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ILM	Internal Limiting Membrane
IMP	Investigational Medicinal Product
[redacted]	[redacted]

IOP	Intraocular Pressure
IRB	Institutional Review Board
IVT	Intravitreal
IWRS	Interactive Web Response System
[redacted]	[redacted]
LOCF	Last Observation Carried Forward
mg	Milligram
µL	Microlitre
mL	Millilitre
µm	Micrometre
mm	Millimetre
mM	Millimolar
mmHg	Millimetre of Mercury
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
OCTA	Optical Coherence Tomography Angiography
PDR	Proliferative Diabetic Retinopathy
PIS	Patient Information Sheet
PRN	Pro Re Nata
QTL	Quality Tolerance Limit
RPE	Retinal Pigment Epithelium
RTSM	Randomisation and Trial Supply Management
Rx	Treatment
SAE	Serious Adverse Event
[redacted]	[redacted]
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
VEGF	Vascular Endothelial Growth Factor

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