A Phase 1 Study of THR-687: An Integrin Antagonist for the Treatment of Diabetic Macular Edema (DME)

Angiogenesis, Exudation, and Degeneration 2020
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Relevant Financial Disclosures

- OXURION: Consultant and Research Support
Integrin Receptors: Subclasses

RGD integrin receptors implicated in multiple disease hallmarks of DR and wet AMD

**ANGIOGENESIS**
- **RGD:** $\alpha_V\beta_3, \alpha_V\beta_5, \alpha_V, \alpha_5\beta_1$
- **Leukocyte:** $\alpha_4\beta_1(-7), \alpha_4\beta_2, \alpha_M\beta_2$
- **Laminin:** $\alpha_3\beta_1$

**PERMEABILITY**
- **RGD:** $\alpha_V\beta_3, \alpha_V\beta_5, \alpha_5\beta_1$
- **Leukocyte:** $\alpha_4\beta_1(-7), \alpha_4\beta_2, \beta_2$
- **Laminin:** $\alpha_3\beta_1$

**INFLAMMATION**
- **RGD:** $\alpha_V\beta_3, \alpha_V\beta_5, \alpha_5\beta_1$
- **Leukocyte:** $\alpha_4\beta_1(-7), \alpha_4\beta_2, \alpha_M\beta_2$
- **Laminin:** $\alpha_3\beta_1$

**FIBROSIS**
- **RGD:** $\alpha_V\beta_3, \alpha_V\beta_5, \alpha_V\beta_6, \alpha_5\beta_1$
- **Collagen:** $\alpha_2\beta_1, \alpha_1\beta_1$
- **Laminin:** $\alpha_6\beta_1, \alpha_3\beta_1$

Abbreviation(s): RGD, arginylglycylaspartic acid

1 Friedlander et al., 1996; Hamnes et al., 1996; Umeda et al., 2006; Wilkinson-Berka et al., 2006; Fu et al., 2007; Santulli et al., 2008
2 Joussen et al., 2004; Santulli et al., 2008; Iliaki et al., 2009; Lima e Silva et al., 2009; Rao et al., 2010; Hakanpaa et al., 2014; Park et al., 2014
3 Joussen et al., 2004; Santulli et al., 2008; Iliaki et al., 2009; Kanda et al., 2012; Rao et al., 2010; Hirasawa et al., 2016
4 Robbins et al., 1994; Ning et al., 2008; Zahn et al., 2010; Blasco-Mezquita et al., 2011; Lipson et al., 2012; Wang et al., 2012
THR-687: A Pan-RGD Integrin Antagonist

Integrin antagonists work both upstream and downstream of VEGF; hence, they have a potential broader efficacy

- THR-687 is a novel, potent RGD integrin antagonist\(^1\)
- Inhibition of integrins targets multiple processes involved in pathological angiogenesis and vascular leakage
- THR-687 has a broad therapeutic potential:
  - Diabetic retinopathy (DR) with and without diabetic macular edema (DME)
  - Wet (neovascular) age-related macular degeneration

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RGD, arginylglycylaspartic acid; VEGF, vascular endothelial growth factor
THR-687: Anti-angiogenic effect

THR-687 potently inhibits angiogenesis-induced leakage in a cynomolgus monkey CNV model

WEEK 2
(after 2 IVT injections)

WEEK 3
(after 3 IVT injections)

Representative FA images

Abbreviation(s): CNV, choroidal neovascularization; IVT, intravitreal
THR-687: Vascular leakage

THR-687 potently inhibits vascular leakage in a diabetic rat STZ model

Analysis: 4 weeks after diabetes onset: FITC-BSA perfusion to assess retinal permeability

Vascular leakage

Mean ± SEM
N=4-16
* p<0.05;
** p<0.01;
*** p<0.001

Abbreviation(s): FITC-BSA, Fluorescein isothiocyanate labelled bovine serum albumin; STZ, streptozotocin
Hu TT et al. Poster Presented at EVER 2019, Nice, France.
**THR-687-001: Study Design**

Open-label, Multicenter, 3+3 Dose-Escalation Study

**Total N = 12 subjects**
- Age ≥ 18 years
- CI- DME; CST ≥ 320 µm (SD-OCT*)
- BCVA ≤ 62 (20/63) and ≥ 23 letters (20/320)
- History of response to prior anti-VEGF / corticosteroid treatment that in opinion of investigator remains responsive to treatment

Screening

Primary outcome measure

Secondary outcome measures

Study Treatment IVT

- Incidence of DLTs D0–D14
- Incidence of systemic and ocular AEs on D0–M3
- Occurrence of laboratory abnormalities up to the end of the study

- 0.4 mg THR-687 (low dose)
- 1.0 mg THR-687 (middle dose)
- 2.5 mg THR-687 (high dose)

1. **Intraocular inflammation**: ≥ 2+ inflammation on any of the intraocular inflammation grading scales
2. **BCVA**: ≥ 10 ETDRS letter score decrease in BCVA from Baseline
3. **Macular hole**

BCVA, best-corrected visual acuity; CST, central subfield thickness; D, Day; DLT, dose-limiting toxicity; DLT, dose-limiting toxicity; SD-OCT, spectral domain optical coherence tomography
### THR-687-001: Demographics

**All Treated Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Dose N=3</th>
<th>Middle Dose N=3</th>
<th>High Dose N=6</th>
<th>Overall N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>58.0 (9.54)</td>
<td>59.7 (8.08)</td>
<td>56.8 (13.14)</td>
<td>57.8 (10.41)</td>
</tr>
<tr>
<td>Min, max</td>
<td>47, 64</td>
<td>51, 67</td>
<td>38, 72</td>
<td>38, 72</td>
</tr>
</tbody>
</table>

- Most subjects were male and white.
- Average age was 57.8 years and there were no relevant differences between the dose groups.
### THR-687-001: Baseline Ocular Characteristics in the Study Eye (1/2)

**All Treated Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Dose N=3</th>
<th>Middle Dose N=3</th>
<th>High Dose N=6</th>
<th>Overall N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCVA (ETDRS letters)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.3 (2.08)</td>
<td>54.7 (2.31)</td>
<td>55.7 (8.26)</td>
<td>56.3 (6.02)</td>
</tr>
<tr>
<td>Median</td>
<td>60.0</td>
<td>56.0</td>
<td>58.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>57, 61</td>
<td>52, 56</td>
<td>39, 61</td>
<td>39, 61</td>
</tr>
<tr>
<td><strong>CST (µm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>557.0 (178.41)</td>
<td>612.3 (77.20)</td>
<td>499.0 (154.82)</td>
<td>541.8 (142.08)</td>
</tr>
<tr>
<td>Median</td>
<td>658.0</td>
<td>576.0</td>
<td>510.0</td>
<td>568.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>351, 662</td>
<td>560, 701</td>
<td>320, 718</td>
<td>320, 718</td>
</tr>
</tbody>
</table>

- There was no relevant imbalance between the groups for BCVA
- CST was lower in the high dose group compared to the other dose groups.
THR-687-001: Baseline Ocular Characteristics in the Study Eye (2/2)

All Treated Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Dose N=3</th>
<th>Middle Dose N=3</th>
<th>High Dose N=6</th>
<th>Overall N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of DR, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>PDR</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td><strong>Prior Treatment for DME, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td><strong>Prior laser, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal / grid laser</td>
<td>1</td>
<td>2*</td>
<td>1</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>PRP</td>
<td>1</td>
<td>2*</td>
<td>0</td>
<td>3 (25.0)</td>
</tr>
</tbody>
</table>

- Overall most subjects had moderate NPDR; subjects in the high dose group had less severe DR
- All subjects received prior treatment with anti-VEGF (3-19 injections prior to enrolling in the study)

Type of DR corresponds to Diabetic Retinopathy Scale assessed by CRC using Color Fundus Photography; NPDR, nonproliferative diabetic retinopathy; PRP, panretinal photocoagulation; * Both subjects had focal/grid laser and PRP;
## THR-687-001: Safety Overview

### All Treated Subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>Low Dose N=3</th>
<th>Middle Dose N=3</th>
<th>High Dose N=6</th>
<th>Overall N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n [E]</td>
<td>n [E]</td>
<td>n [E]</td>
<td>n (%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DLT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to withdrawal from study</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No DLTs occurred at any dose
- No SAEs developed
- There was one subject in each dose group with a treatment-related AE(s)
## THR-687-001: Adverse Events in the Study Eye

### All Treated Subjects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Low Dose N=3</th>
<th>Middle Dose N=3</th>
<th>High Dose N=6</th>
<th>Overall N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n [E]</td>
<td>n [E]</td>
<td>n [E]</td>
<td>n (%)</td>
</tr>
<tr>
<td>Diabetic retinal edema</td>
<td>0</td>
<td>1 [1]</td>
<td>2 [2]</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>1 [1] ^a</td>
<td>1 [1] ^a</td>
<td>0</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>0</td>
<td>0</td>
<td>1 [1] ^a</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>1 [1] ^a</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>0</td>
<td>1 [1]</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0</td>
<td>0</td>
<td>1 [1]</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

### Notes:
- All AEs deemed treatment-related by the Investigator, were ocular and likely injection procedure related.
- Other AEs were likely due to the injection procedure, underlying disease progression, or concomitant diseases.
- No cases of endophthalmitis or intraocular inflammation.

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E, number of events; n, number of subjects in category; N, number of subjects with data available

^a Deemed treatment-related (drug and/or procedure) by the Investigator.
All Treated Subjects

**THR-687-001: First Rescue Treatment**

**Rescue criteria:**
Standard-of-care treatment for DME can be administered in the study eye if deemed necessary by the Investigator and if at least one of the following criteria is met:

- ≥ 10 ETDRS letter score loss in BCVA from baseline, with accumulation of additional retinal fluid on SD-OCT, as assessed by the Investigator
- ≥ 50μm increase in CST from baseline on SD-OCT, as assessed by the Investigator

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**Study visit**

- **Low dose (N=3)**
- **Middle dose (N=3)**
- **High dose (N=6)**

**Subjects (n):**

- D7, M1, M2, M3

**Graphs:**

- Yellow bar: Ranibizumab
- Green bar: Aflibercept
- Red bar: Bevacizumab

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D, Day; M, Month
A rapid onset of action in mean BCVA was observed as of Day 1 with 3.1 letters gain.
Mean BCVA gain was the highest at Month 1, with 9.2 letters.
Mean BCVA gain was maintained post-injection, with a mean gain of 8.3 letters at Month 3.

Value before rescue carried forward; D, Day; M, Month; SE, standard error;
BCVA improvement was most pronounced in the high dose group, with a mean BCVA gain of 12.5 letters at Month 3.

Value before rescue carried forward; D, Day; M, Month;
THR-687-001: Mean Change in CST From Day 1 (Accounted for Rescue)\textsuperscript{a}

All Treated Subjects, Overall

- Overall, marginal impact on mean CST was noted up to Month 1, followed by a return to baseline level until Month 3

SD-OCT not assessed at Day 0; \textsuperscript{a}Value before rescue carried forward;
D, Day; M, Month; SE, standard error;
A pronounced mean decrease in CST was noted in the high dose, with a decrease of 106 µm at Day 14.
THR-687-001: Change in BCVA From Day 0 & CST From Day 1 per Subject

**High Dose**

- A persistent and pronounced increase in BCVA was seen in 3 subjects (1, 4, 5), with no need for rescue treatment.
- CST decrease was clinically relevant for 3 subjects (4, 5, 6) and was maintained up to at least Month 2.

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SD-OCT not assessed at Day 0; D, Day; M, Month; R, rescue treatment;
THR-687-001: IMPORTANT TAKE-HOME MESSAGES

• THR-687 is safe and well-tolerated: no DLTs, no SAEs occurred

• Has a rapid onset of action resulting in significant BCVA gain and durability of mean BCVA

• The high dose (2.5mg) had the most pronounced BCVA improvement and CST reduction