Results of a Phase 1, Open-Label, Dose-Escalation Study of THR-149 for the Treatment of DME

Dr. Pravin Dugel
London · 15 September 2019
Unmet Medical Need in DME

- Anti-VEGFs are the 1st line treatment for DME

- Up to 40% patients do not adequately respond to anti-VEGF treatment in terms of BCVA and / or CST improvement

  ⇒ Other pathways involved in development of DME

- Potential side effects after a long-standing VEGF blockade *
  
  ✓ VEGF acts as a survival factor for choriocapillaris, retinal neurons, and retinal pigment epithelium
  
  ✓ Efficacious inhibition of VEGF can lead to higher incidence of retinal geographic atrophy in the clinic

Targeting Plasma Kallikrein in DME

THR-149 is a Potent Reversible Peptide Inhibitor of Plasma Kallikrein (PKal)

Targeting PKal offers a **VEGF-independent mechanism** for inhibiting DME:

- PKal/Kinin System is upregulated under diabetic conditions
- In preclinical models of diabetes, PKal mediates vascular hyperpermeability, leukostasis, inflammation, and micro-hemorrhages
- Evidence for clinical efficacy after PKal inhibition hereditary angioedema and DME
Biochemical Characterization of THR-149

Inhibition of Bradykinin Formation in Kaolin-Activated Human Plasma / Vitreous

THR-149 blocks release of bradykinin in plasma and vitreous

Teufel et al. 2018 J. Med. Chem. 61, 2823–36
Rationale for Targeting PKal in DME

Potential target for THR-149 + anti-VEGF Combo-therapy

Any level VEGF
Any level PKal

Potential target for THR-149 Mono-therapy

Low VEGF
High PKal

Start building clinical evidence with THR-149 mono-therapy

Adapted: Kita et al. 2015 Diabetes 64:3588–99
THR-149-001: Study Overview

3+3 Dose-Escalation Study

Total N = 12 patients

- Cl-DME CST >320 µm (Spectralis SD-OCT)
- BCVA ≤ 62 and ≥ 23 letters
- History of response to prior anti-VEGF / corticosteroid treatment

Study Treatment IVT

Screening

Primary outcome measure

Secondary outcome measures

• Incidence of dose-limiting toxicities Day 0-14

MONTH 2

DAY 0 1 7 DAY 14 MONTH 1 MONTH 2 MONTH 3

Incidence of systemic and ocular adverse events up to Month 3
• Occurrence of laboratory abnormalities up to Month 3

0.005mg THR-149 (low dose)
0.022mg THR-149 (middle dose)
0.13mg THR-149 (high dose)
THR-149-001: Baseline Ocular Characteristics in the Study Eye

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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCVA (ETDRS letters)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>46.0 (9.17)</td>
<td>46.7 (8.62)</td>
<td>43.0 (12.59)</td>
</tr>
<tr>
<td>Median</td>
<td>44.0</td>
<td>45.0</td>
<td>43.5</td>
</tr>
<tr>
<td>Min, Max</td>
<td>38, 56</td>
<td>39, 56</td>
<td>25, 58</td>
</tr>
<tr>
<td><strong>CST (µm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>497.7 (70.04)</td>
<td>539.3 (35.95)</td>
<td>529.5 (120.60)</td>
</tr>
<tr>
<td>Median</td>
<td>533.0</td>
<td>551.0</td>
<td>585.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>417, 543</td>
<td>499, 568</td>
<td>373, 626</td>
</tr>
</tbody>
</table>

No relevant imbalances between treatment arms for Baseline BCVA and CST
## THR-149-001: 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>DLT</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>
</tr>
<tr>
<td>Treatment-related (drug and / or procedure) AE</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- 3 SAEs (non-ocular, nontreatment-related) in 1 subject
- No DLTs
- 1 treatment-related ocular AE
THR-149-001: 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>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior chamber inflammation</td>
<td>0</td>
<td>1 ^a</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Corneal disorder</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diabetic retinal edema</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Eye pain</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Macular fibrosis ^b</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

^b Epiretinal membrane (2 events in 1 subject)

- 1 ocular AE related to study treatment (likely injection procedure) in the middle dose
- All ocular AEs were likely due to the injection procedure, underlying disease progression, or concomitant diseases
THR-149-001: Mean Change in BCVA From Baseline (Accounted for Rescue)\textsuperscript{a}

All Treated Subjects, Overall

Mean BCVA gain was fast and maintained until end of study

Mean change in BCVA (SE) from Baseline (ETDRS letters)

Study visit

BL, D1, D7, D14, M1, M2, M3

Overall mean BCVA at Baseline was 44.7 ETDRS letters

\textsuperscript{a}Value before rescue carried forward
THR-149-001: Mean Change in CST From Baseline (Accounted for Rescue)\textsuperscript{a}

All Treated Subjects, Overall

- Marginal impact on mean CST at Day 1 followed by increase until study end
- Mean CST change was minimal and within the variability of measurement

Overall mean CST at Baseline was 524\textmu m

\textsuperscript{a}Value before rescue carried forward
Discussion: Understanding the disconnect between BCVA and CST in study THR-149-001

**Existing public data**

- Known disconnect between BCVA and CST in DME patients:
  - DRCR.net, Ophthalmology 2007
  - Prior clinical data with PKal inhibition in DME

**Ongoing quantitative assessment of THR-149-001 data**

- Link between **Baseline** characteristics (DR duration, macular volume, PKal levels in aqueous humor) and BCVA / CST response
- Link **over time** between anatomic parameters (other than CST) with BCVA response
- Impact of VEGF: VEGF levels determination in aqueous humor samples
- Evaluation aqueous humor samples for retinal stress markers

**Ongoing qualitative assessment of THR-149-001 data**

- Image interpretation by experts
Link between Baseline Characteristics and BCVA Response

Study THR-149-001: Exploratory Statistical Analysis

- BL BCVA, macular volume and years since DR are more predictive than BL CST or PKal levels for BCVA response
- Better BL BCVA, lower macular volume and longer duration of DR indicative for BCVA response
In the BCVA responders, macular volume was maintained over time.

* \( \geq 10 \) letters increase in at least 2 consecutive visits (no rescue)
Discussion: Understanding Disconnect between Reduction of Retinal Vascular Leakage in Pre-Clinical Model versus CST Data

Clinical Study

**Pre-Clinical Experiments**

- Revisit the thickness of the individual retinal layers and visual performance (optomotor) in diabetic rat model
- Detailed study of retinal fluid homeostasis versus vascular permeability / leakage
THR-149-001: Key Take Away Messages

- THR-149 is **safe** and **well tolerated**:
  - No DLTs
  - No ocular SAEs
  - 1 treatment-related ocular AE - considered related to the injection procedure

- Mean BCVA gain was **fast** and **maintained** until end of study:
  - Day 1: 3.9 letters
  - Max at Day 14: 7.5 letters
  - Month 3: 6.4 letters

- **Macular volume** at BL seems to be indicative for BCVA response, and amongst the BCVA responders macular volume was maintained over time

Overall gains noted in BCVA, and improvement in CST in some subjects are encouraging and warrant further clinical research with multiple injections of THR-149.