# KALAHARI: Part A Results of the Phase 2 Study of THR-149, a Plasma Kallikrein Inhibitor, in Subjects with DME who Respond Suboptimally to anti-VEGF Treatment

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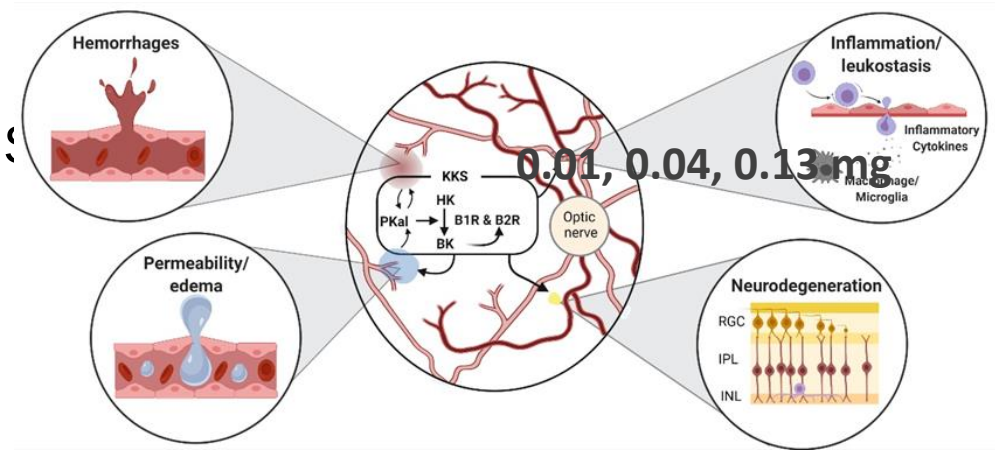
# Financial Disclosures

- This work was supported by Oxurion NV from whom trial sites received research support

# THR-149: Highly Potent Plasma Kallikrein Inhibitor for DME

Selective and stable peptide



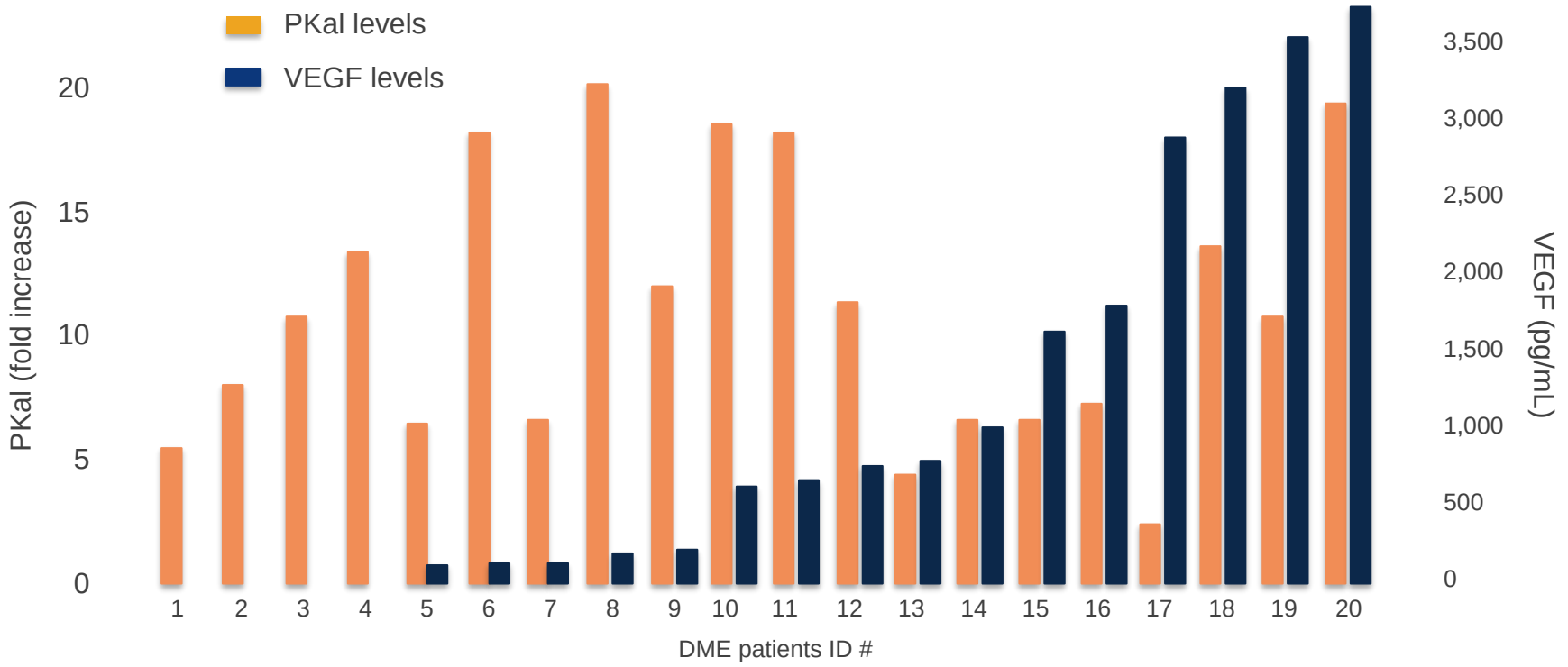

**0.01, 0.04, 0.13 mg**

- Plasma Kallikrein is a mediator of vascular leakage, inflammation, microhemorrhages and neurodegeneration.
- Human vitreous shows elevated PKal levels in DME patients.
- THR-149, a potent and selective PKal inhibitor[1], has the potential to reduce the hallmarks of DME.

Abbreviation(s): BK, bradykinin; B1R,bradykinin receptor 1; B2R, bradykinin receptor 2; DME, diabetic macular edema; HK, High molecular weight kininogen; INL, inner nuclear layer; IPL, inner plexiform layer; KKS, kinin kallikrein system; PK, PreKallikrein; PKal, plasma kallikrein; RGC, retinal ganglion cell

Source(s): [1] Teufel et al. *J Med Chem* 2018;61(7):2823-2836; Sun JK & Kampol LM. *Ophthamic Res* 2019;62:225-230

# THR-149: Rationale for targeting plasma kallikrein in DME




- PKal is a key, VEGF-independent driver of DME
- PKal inhibitors have potential in the treatment of suboptimal responders to SoC

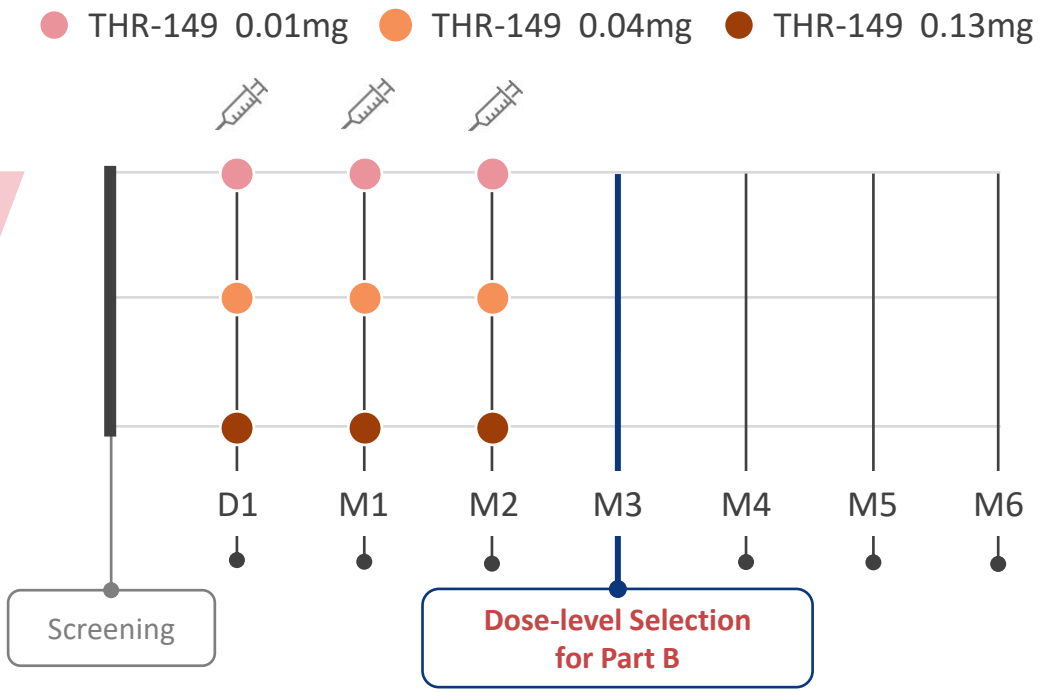
Abbreviations: DME, diabetic macular edema; PKal, plasma kallikrein; SoC standard of care; VEGF, vascular endothelial growth factor

Source(s): adapted from Kita T et al. Diabetes 2015;64:3588-3599

# Study Design

**Part A • Dose level selection THR-149**

N≈18, Rando 1:1:1




**DME patients with suboptimal response to prior anti-VEGF and who may benefit from a new mechanism of action with:**

- CST ≥ 320µm (OCT)
- BCVA ≤ 73 and ≥ 39 ETDRS letters
- ≥ 5 anti-VEGF injections
- Last injection aflibercept 3-8 weeks prior to screening

**Key endpoints:**

- Systemic & ocular AEs and SAEs
- Mean change in BCVA ETDRS letter score from Baseline
- Mean change in CST from Baseline

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; SAE, serious adverse event; VEGF, vascular endothelial growth factor

# Demographics

| Characteristic | THR-149 0.01mg (N=6) | THR-149 0.04mg (N=6) | THR-149 0.13mg (N=8) | Overall (N=20) |
|---|---|---|---|---|
| **Gender, n (%)** | | | | |
| **Male** | 5 | 3 | 4 | 12 (60) |
| **Female** | 1 | 3 | 4 | 8 (40) |
| **Race, n (%)** | | | | |
| **White** | 5 | 6 | 8 | 19 (95) |
| **Black or African American** | 1 | 0 | 0 | 1 (5) |
| **Age (years)** | | | | |
| **Mean (SD)** | 64.7 (9.33) | 66.7 (10.17) | 60.0 (10.90) | 63.4 (10.13) |

- Subject demographics were similar in the 3 dose groups

Per Protocol Set used for Demographics

Abbreviations: n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set; SD, Standard Deviation

# Baseline Disease Characteristics in the Study Eye

| Characteristic | THR-149 0.01mg (N=6) | THR-149 0.04mg (N=6) | THR-149 0.13mg (N=8) | Overall (N=20) |
|---|---|---|---|---|
| **DR Severity, n (%)** | | | | |
| **Mild/Moderate NPDR** | 5 | 4 | 8 | 17 (85) |
| **Moderately Severe NPDR** | 1 | 1 | 0 | 2 (10) |
| **Severe NPDR** | 0 | 1 | 0 | 1 (5) |
| **Time since First Diagnosis of DR (years)** | | | | |
| **Median** | 1.05 | 3.10 | 2.05 | 2.40 |
| **Total number of anti-VEGF Injections for DME prior to Screening** | | | | |
| **Mean (SD)** | 11.2 (8.18) | 11.5 (4.14) | 10.0 (4.07) | 10.8 (5.36) |
| **Number of anti-VEGF Injections for DME during the Last Year prior to Screening, n (%)** | | | | |
| **2 - 5** | 2 | 0 | 2 | 4 (20) |
| **> 5** | 4 | 6 | 6 | 16 (80) |

- DR severity was mild or moderate for most subjects
- In the middle dose, 2 subjects had more severe DME and longer duration of DR
- 80% of the subjects received more than 5 anti-VEGF treatments in the year preceding screening

Per Protocol Set used for Baseline Characteristics / * Based on SD-OCT, assessed by the CRC

Abbreviations: BCVA, Best-corrected Visual Acuity; CRC, Central Reading Centre; CST, Central Subfield Thickness; n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set; SD, Standard Deviation

# Baseline Ocular Characteristics in the Study Eye

| Characteristic | THR-149 0.01mg (N=6) | THR-149 0.04mg (N=6) | THR-149 0.13mg (N=8) | Overall (N=20) |
|---|---|---|---|---|
| **BCVA (ETDRS letters)** | | | | |
| **Mean (SD)** | 65.3 (7.03) | 62.5 (10.52) | 61.0 (13.62) | 62.8 (10.67) |
| **BCVA Category, n (%)** | | | | |
| **≤ 63 letters** | 3 | 3 | 4 | 10 (50) |
| **> 63 letters** | 3 | 3 | 4 | 10 (50) |
| **CST* (µm)** | | | | |
| **Mean (SD)** | 465.5 (81.66) | 470.7 (101.19) | 421.9 (83.01) | 449.6 (86.78) |
| **CST* Category, n (%)** | | | | |
| **≤ 400µm** | 1 | 1 | 4 | 6 (30) |
| **> 400µm** | 5 | 5 | 4 | 14 (70) |

- Baseline BCVA was balanced across the 3 dose groups
- On average, baseline CST was slightly lower in the high dose group

Per Protocol Set used for Baseline Characteristics / * Based on SD-OCT, assessed by the CRC

Abbreviations: BCVA, Best-corrected Visual Acuity; CRC, Central Reading Centre; CST, Central Subfield Thickness; n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set; SD, Standard Deviation

# Adverse Events in the Study Eye

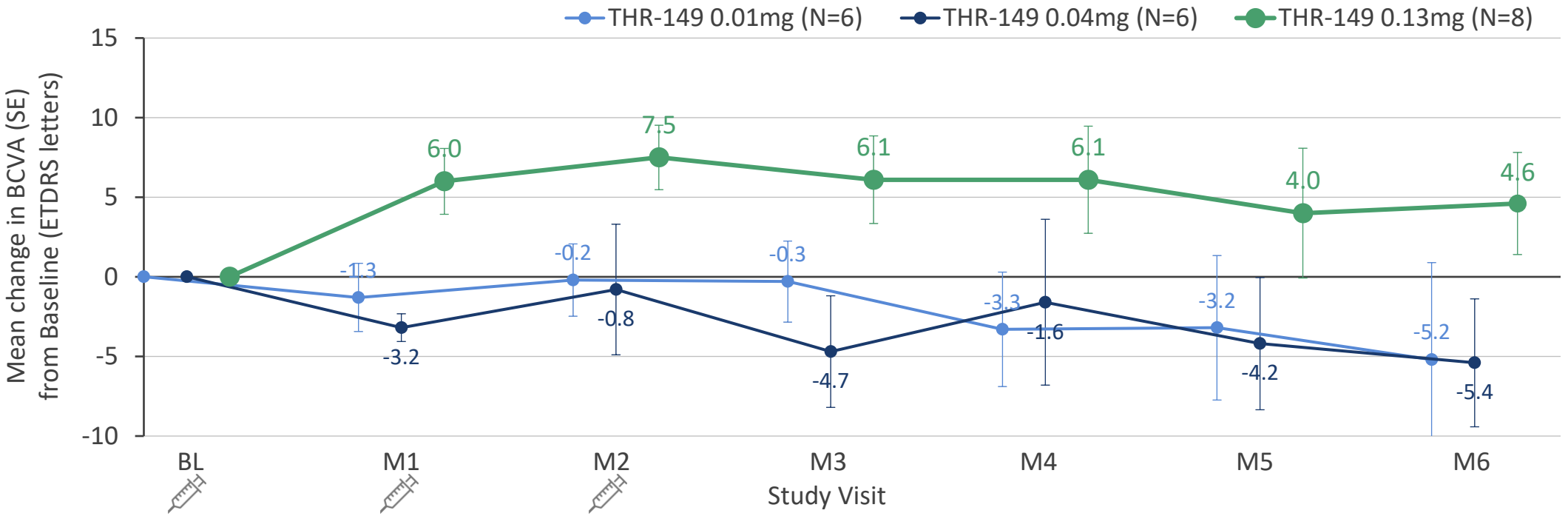
| Adverse Event | THR-149 0.01mg (N=7) | | THR-149 0.04mg (N=7) | | THR-149 0.13mg (N=9) | |
|---|---|---|---|---|---|---|
| | Up to M3 | M3 to EOS | Up to M3 | M3 to EOS | Up to M3 | M3 to EOS |
| | n [E] | n [E] | n [E] | n [E] | n [E] | n [E] |
| **Diabetic Retinal Edema** | 1 [1]** | 1 [1] | 1 [1] | 0 | 0 | 0 |
| **Dry Eye** | 0 | 0 | 0 | 1 [1] | 0 | 0 |
| **Intraocular Pressure Increased** | 0 | 0 | 1 [1]* | 0 | 0 | 0 |
| **Retinal Aneurysm** | 0 | 0 | 0 | 0 | 1 [1] | 0 |
| **Retinal Haemorrhage** | 0 | 0 | 0 | 1 [1] | 0 | 0 |
| **Retinal Pigment Epithelial Tear** | 0 | 0 | 0 | 0 | 0 | 1 [1] |
| **Visual Acuity Reduced** | 1 [1] | 0 | 1 [1] | 0 | 0 | 0 |
| **Vitreous Haemorrhage** | 1 [1] | 0 | 0 | 0 | 0 | 0 |

- No serious AEs occurred; no intraocular inflammation was reported
- All AEs were of mild to moderate intensity
- One AE was deemed related to IMP and 1 AE to the injection procedure by the investigator
- No increase in AE incidence was noted with increasing dose and number of injections

All Treated Set used for Safety / * Related to the injection procedure; ** Related to the IMP

Abbreviations: AE, Adverse Event; E, Number of Events; EOS, End of Study; IMP, Investigational Medicinal Product; M, Month; n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set

# Mean Change in BCVA from Baseline [a]




In the high dose group:

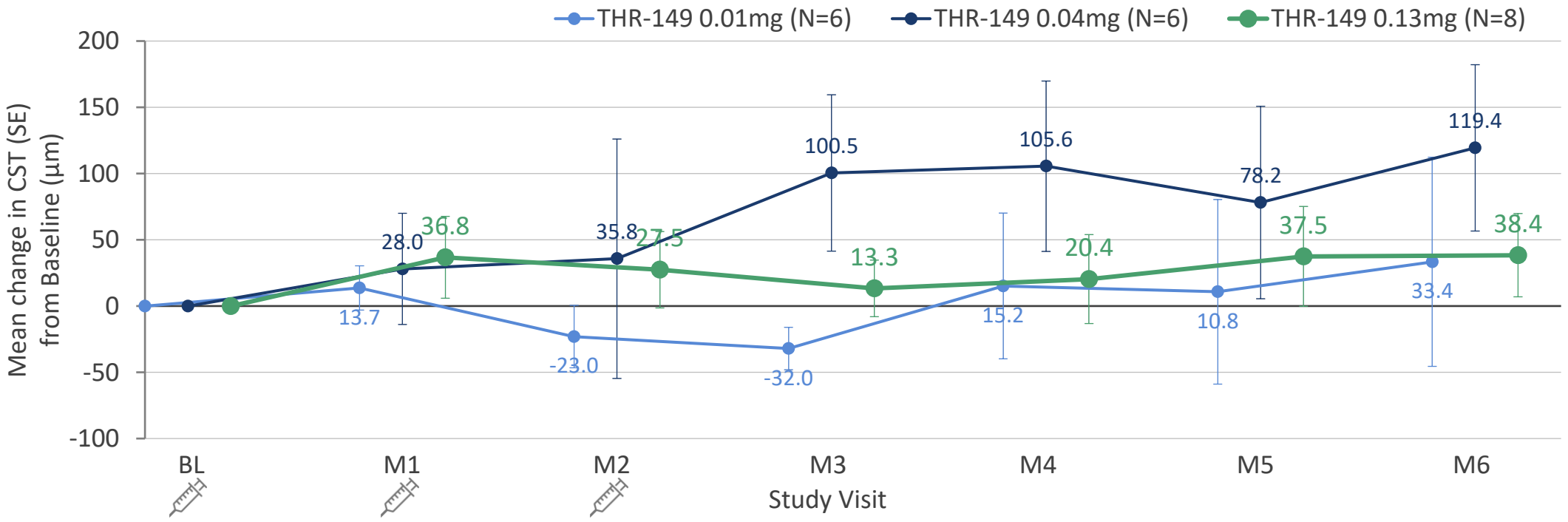
- At Month 3, one month after the third injection, the mean BCVA gain was 6.1 letters (95%CI: -0.4 to 12.6)
- BCVA gain was observed up to Month 6, without the need for rescue treatment

[a] No rescue treatment was given in the high dose group

Per Protocol Set used for Efficacy / [a] Value before rescue carried forward, where applicable

Abbreviations: BCVA, Best-corrected Visual Acuity; BL, Baseline; CI, Confidence Interval; ETDRS, Early Treatment Diabetic Retinopathy Study; M, Month; N, Number of Subjects in the Analysis Set; SE, Standard Error; At Month 4: N=6, 5, 8 respectively; At Month 5 and 6: N=5, 5, 8 respectively

# Mean Change in CST from Baseline [a]




- In the high dose group, stable CST was observed up to Month 6

[a] No rescue treatment was given in the high dose group

Per Protocol Set used for Efficacy / [a] Value before rescue carried forward, where applicable

Abbreviations: CST, Central Subfield Thickness; BL, Baseline; M, Month; N, Number of Subjects in the Analysis Set; SE, Standard Error; At Month 4: N=6, 5, 8 respectively; At Month 5 and 6: N=5, 5, 8 respectively

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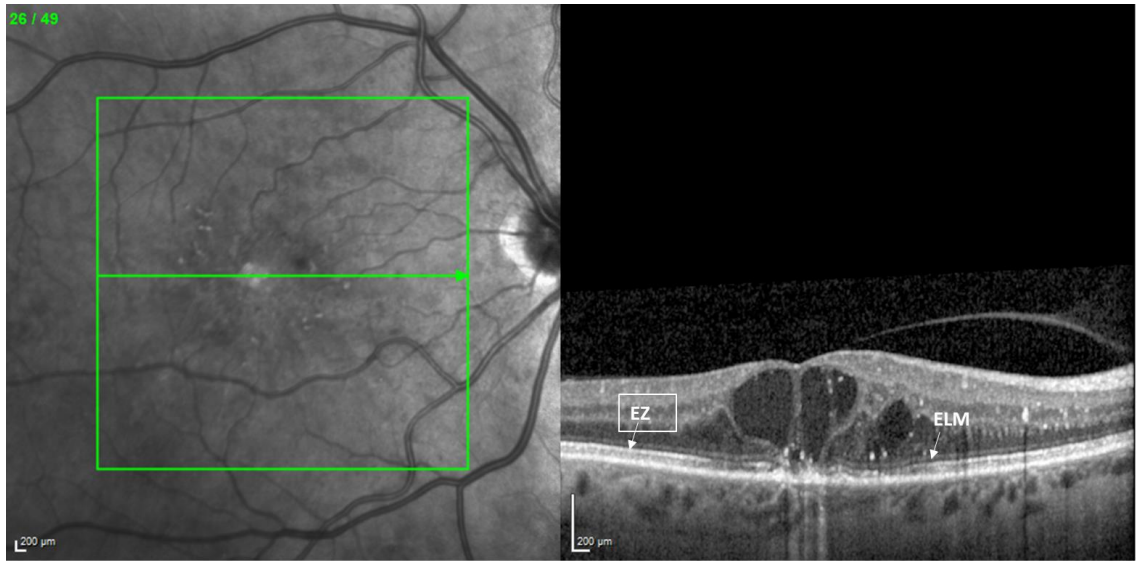
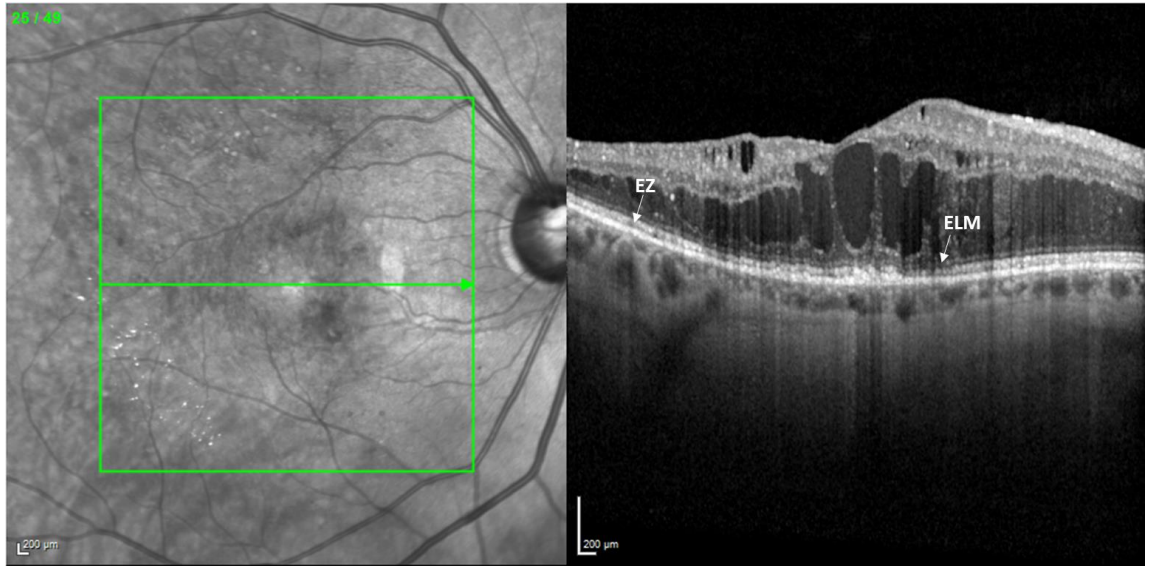
# CRC, masked to clinical data including BCVA, identified 2 subjects with abnormalities on OCT




[a] Abbreviations: BCVA, Best-corrected Visual Acuity; CRC, Central Reading Center; OCT, Optical Coherence Tomography

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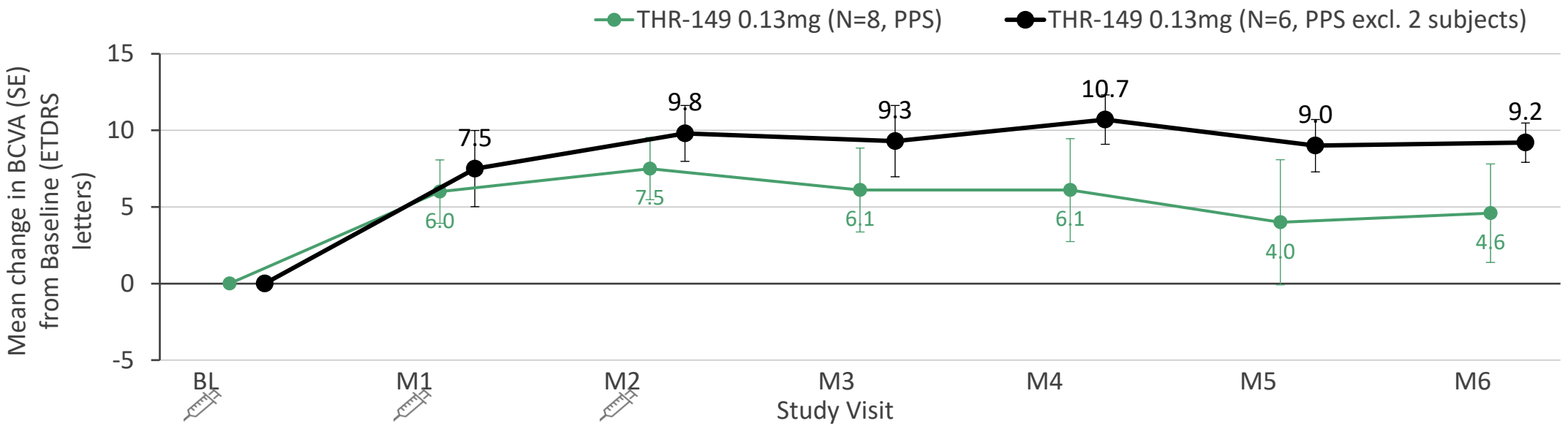
# Mean Change in BCVA from Baseline in the High Dose Group[a]

- **Post-hoc analysis** excluding these 2 subjects showed a mean gain in **BCVA of ≥ 9 letters** up to Month 6
- Part B protocol amended to **refine the target population** and exclude subjects with these abnormalities on OCT




[a] No rescue treatment was given in the high dose group

Abbreviations: BCVA, Best-corrected Visual Acuity; BL, Baseline; CRC, Central Reading Center; ETDRS, Early Treatment Diabetic Retinopathy Study; M, Month; N, Number of Subjects in the Analysis Set; OCT, Optical Coherence Tomography; PPS, Per Protocol Set; SE, Standard Error

# Summary:

- **Multiple IVT injections (up to 3) of THR-149 (0.01, 0.04, 0.13 mg) are safe and well-tolerated**


In the **high dose** group:

- A **mean BCVA gain of 6.1 letters was seen at Month 3**, with gains observed up to Month 6 as well as CST stabilization over the 6-month study period compared to Baseline
- **No need for rescue treatment**
- Post-hoc analysis, excluding 2 subjects with abnormalities on OCT, showed a **mean gain in BCVA of 9.3 letters at Month 3**, which was maintained up to Month 6

- Based on Month 3 Part A data, the high dose of THR-149 was selected for Part B of the KALAHARI study to compare vs. aflibercept
- Part A **data learnings have been implemented** in Part B using an amended study design
- **Part B is currently enrolling globally**



BCVA, Best-Corrected Visual Acuity; CST, Central Subfield Thickness; IVT, Intravitreal; OCT, Optical Coherence Tomography

# Acknowledgements

**Thank You!**

- Patients
- Principal Investigators
- Site Teams
- Ocular Imaging Reading Center

# KALAHARI Part B:

**is currently enrolling globally**

- Patients
- Principal Investigators
- Site Teams
- Ocular Imaging Reading Center