Phase 2 Results of THR-149 in Patients with DME: KALAHARI Study Part A

Arshad M. Khanani, MD, MA
Director of Clinical Research,
Sierra Eye Associates, Reno, NV

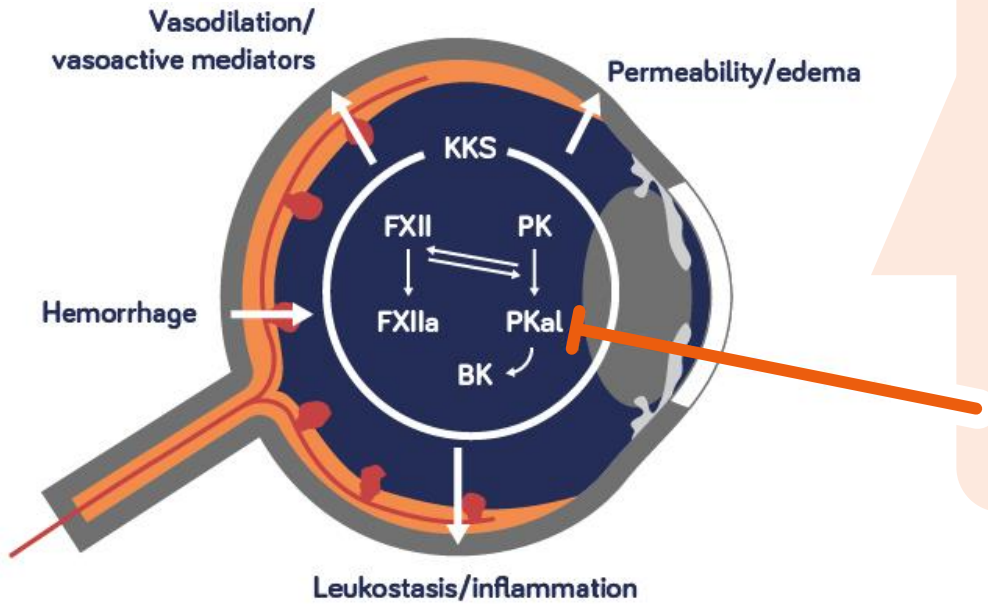
Angiogenesis, Exudation, and Degeneration 2022 • Virtual Edition

KALAHARI

Disclosures

- **Consultant**: Adverum, Aerpio, Alimera, Allergan, Apellis, Asclepix, Aviceda, Bausch and Lomb, Broadwing Bio, Chengdu Kanghong, Cholgene, 4DMT, Dutch Ophthalmic Research Center, Gemini, Genentech, Glaukos, Graybug, Gyroscope, Iveric Bio, Janssen, Kato Pharma, Kodiak, Oculis, Opthea, **Oxurion**, Novartis, Polyphotonix, Recens Medical, Regeneron, Retrotope, Regenxbio, Roche, Surrozen, Thea, Unity Bio
- **Research Support**: Adverum, Apellis, Asclepix, Chengdu Kanghong, 4DMT, Gemini, Genentech, Graybug Vision, Gyroscope, Iveric Bio, Janssen, Kodiak, Neurotech, NGM Bio, Ocular Therapeutix, Oculis, Opthea, **Oxurion**, Novartis, Recens Medical, Regenxbio, Roche, Unity Bio
- **Equity**: Aviceda, Gyroscope, Recens Medical, Retrotope, Polyphotonix
- **Speaker**: Allergan, Genentech, Novartis

THR-149 is a Highly Potent Plasma Kallikrein Inhibitor for DME



- PKal is a clinically validated target for edema, inflammation, and the prevention of microhemorrhages
- PKal is a key driver of DME pathology, independent of VEGF

THR-149 is a selective pKal inhibitor having the potential to treat the 40-50% of patients who respond suboptimally to anti-VEGFs

KALAHARI

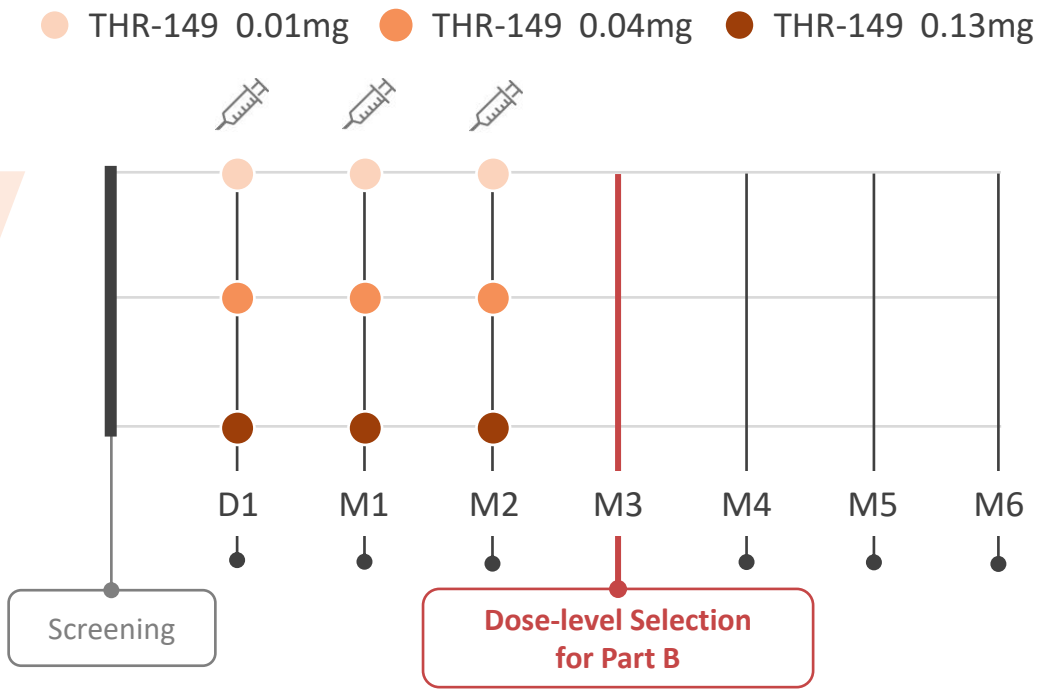
BK, bradykinin; DME, Diabetic Macular Edema; FXII, Factor XII; KKS, Kinin Kallikrein System; PK, PreKallikrein; pKal, Plasma Kallikrein; VEGF, Vascular Endothelial Growth Factor

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

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

KALAHARI

AEs, Adverse Events; BCVA, Best-corrected Visual Acuity; CST, Central Subfield Thickness; D, Day; DME, Diabetic Macular Edema; ETDRS, Early Treatment Diabetic Retinopathy Study; M, Month; N, Number; Rando, Randomization; OCT, Optical Coherence Tomography;

SAEs, Serious Adverse Events; VEGF, Vascular Endothelial Growth Factor

Demographics

- Subject demographics were similar in the 3 dose groups

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)

KALAHARI

Per Protocol Set used for Demographics

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

Baseline Disease Characteristics in the Study Eye

- 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

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)

KALAHARI

Per Protocol Set used for Baseline Characteristics

DME, Diabetic Macular Edema; DR, Diabetic Retinopathy; n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set; NPDR, Nonproliferative Diabetic Retinopathy ; VEGF, Vascular Endothelial Growth Factor

Baseline Ocular Characteristics in the Study Eye

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

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)

Per Protocol Set used for Baseline Characteristics

* Based on SD-OCT, assessed by the CRC

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

KALAHARI

Adverse Events in the Study Eye

- 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

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

All Treated Set used for Safety

* Related to the injection procedure; ** Related to the IMP

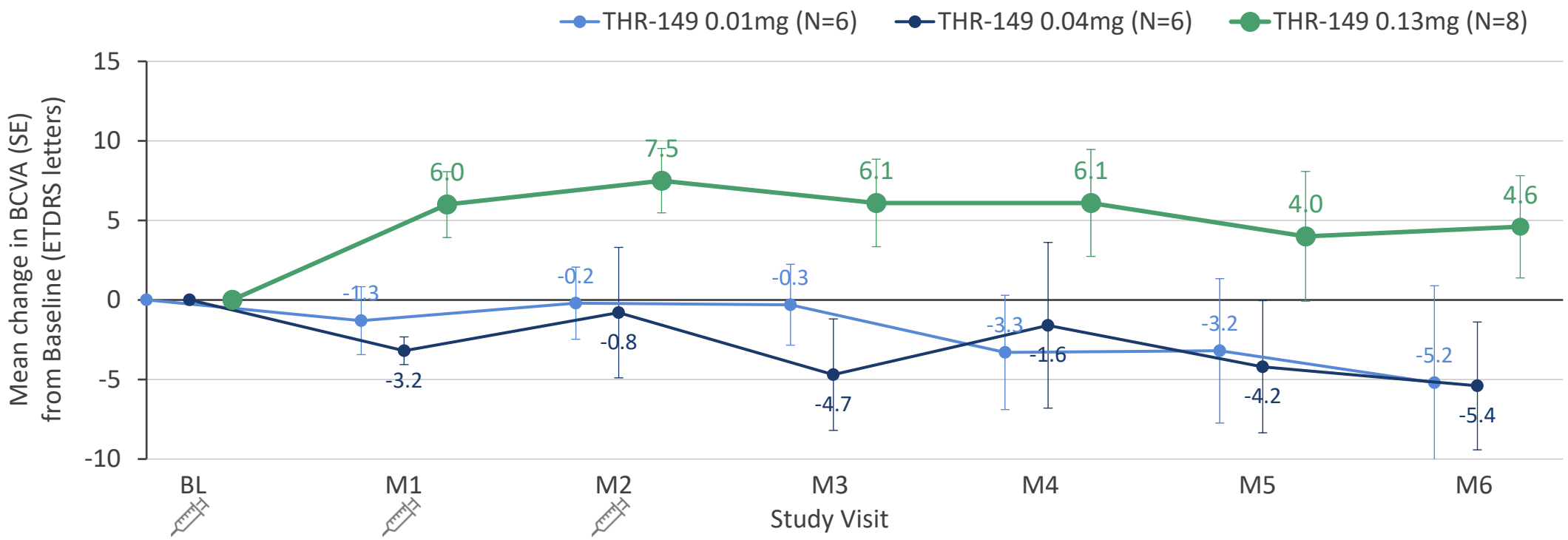
AE, Adverse Event; E, Number of Events; EOS, End of Study; IMP, Investigational Medicinal Product; M, Month; n, Number of Subjects in Category; N, Number of Subjects in the Analysis Set

KALAHARI

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



Per Protocol Set used for Efficacy

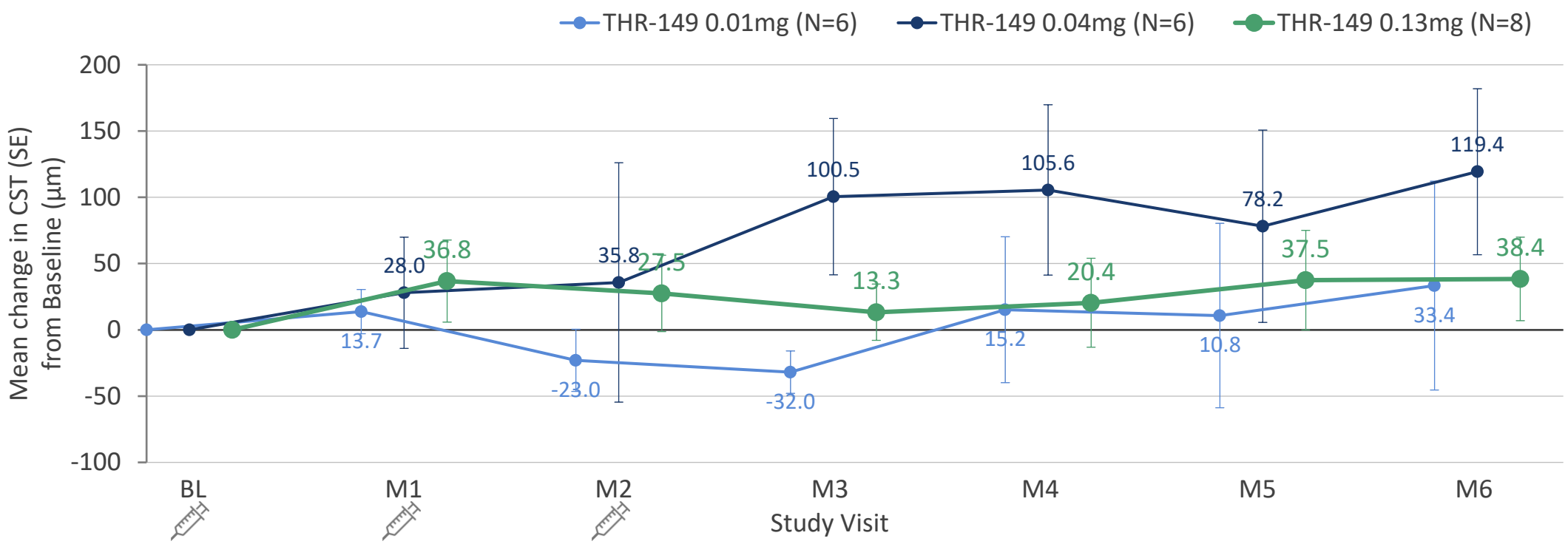
[a] Value before rescue carried forward, where applicable

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

KALAHARI

Mean Change in CST from Baseline [a]

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



Per Protocol Set used for Efficacy

[a] Value before rescue carried forward, where applicable

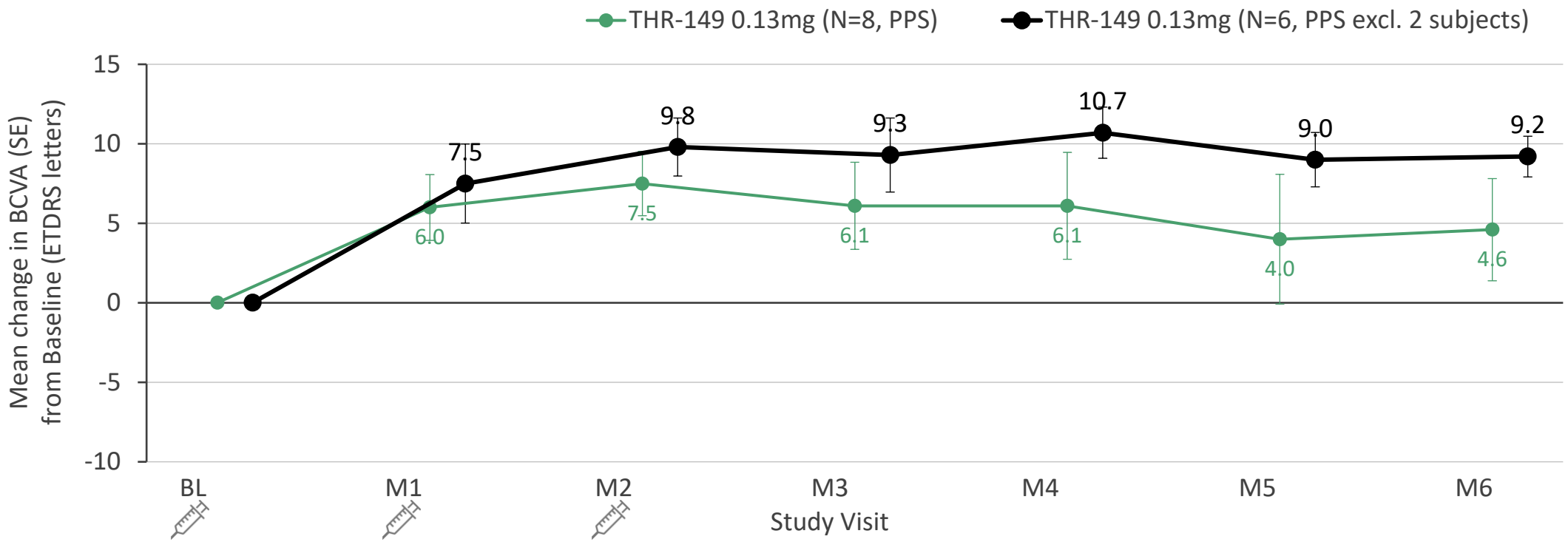
CST, Central Subfield Thickness; BL, Baseline; M, Month; N, Number of Subjects in the Analysis Set; SE, Standard Error; At Month 4: N=6, 5, 8 respectively; At Month 5 and 6: N=5, 5, 8 respectively

KALAHARI

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

Post-hoc Analysis

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

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 three) of THR-149 are safe and well-tolerated 0.01,0.04,0.13**

In the **high dose** group:

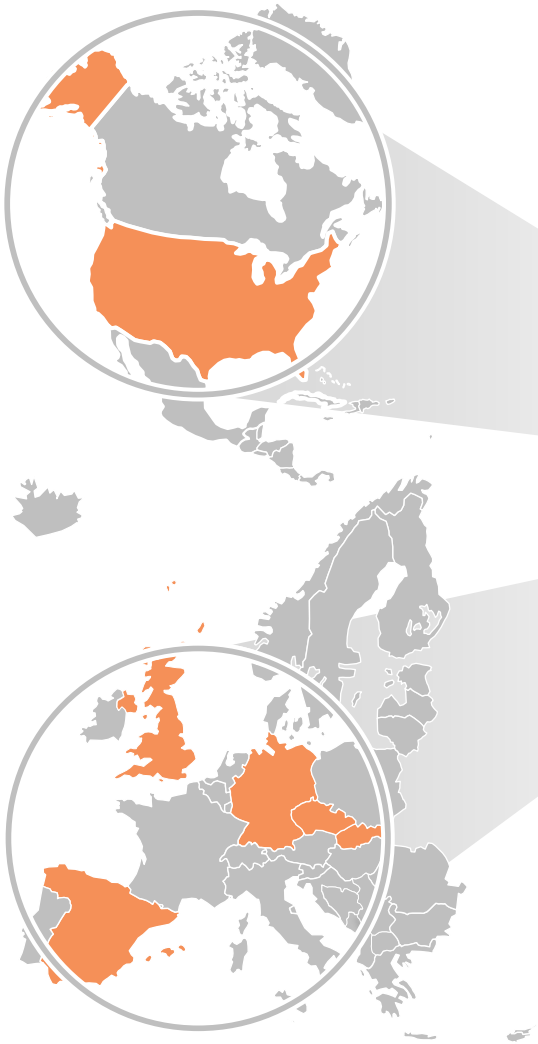
- A **mean BCVA gain of 6.1 letters was seen at Month 3**, with gains observed up to Month 6 as well as CST stabilization over the 6-month study period compared to Baseline
- **No need for rescue treatment**
- Post-hoc analysis, excluding 2 subjects with abnormalities on OCT, showed a **mean gain in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

KALAHARI

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

Acknowledgements for Part A

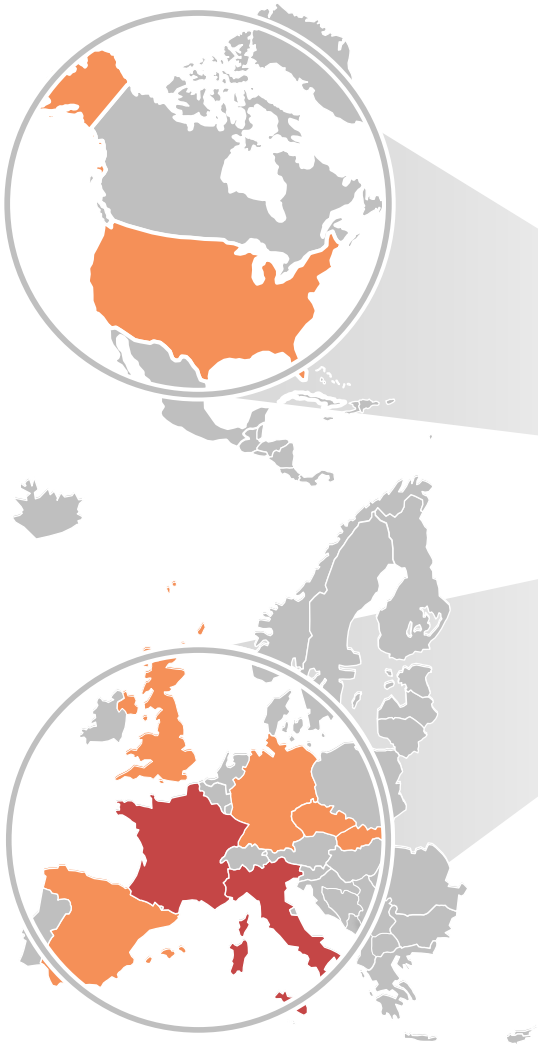


Thank You!

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

KALAHARI

KALAHARI Part B



is currently enrolling globally

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

KALAHARI