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

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Unmet Medical Need in DME

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

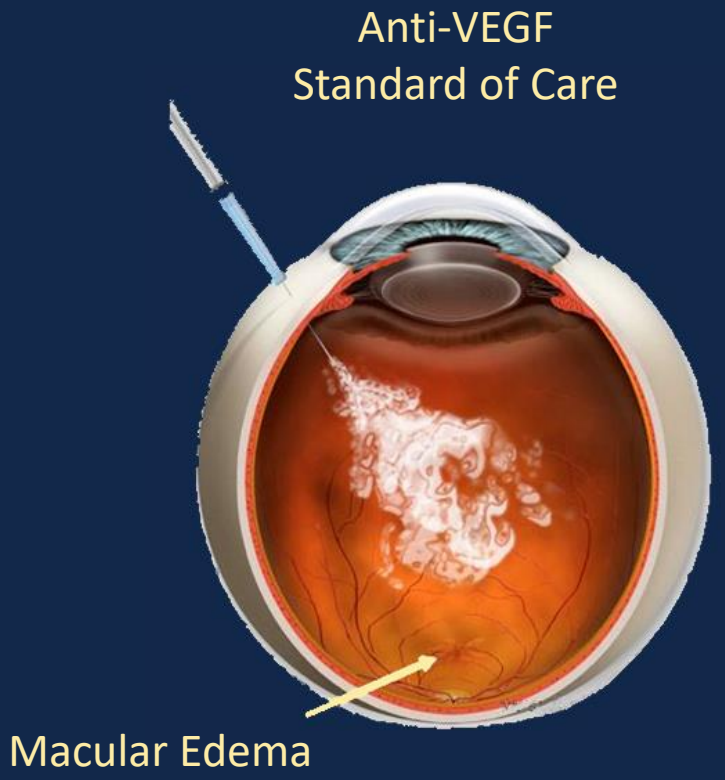
- Up to 40% patients do not adequately respond to anti-VEGF treatment in terms of BCVA and / or CST improvement

  ⇒ 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



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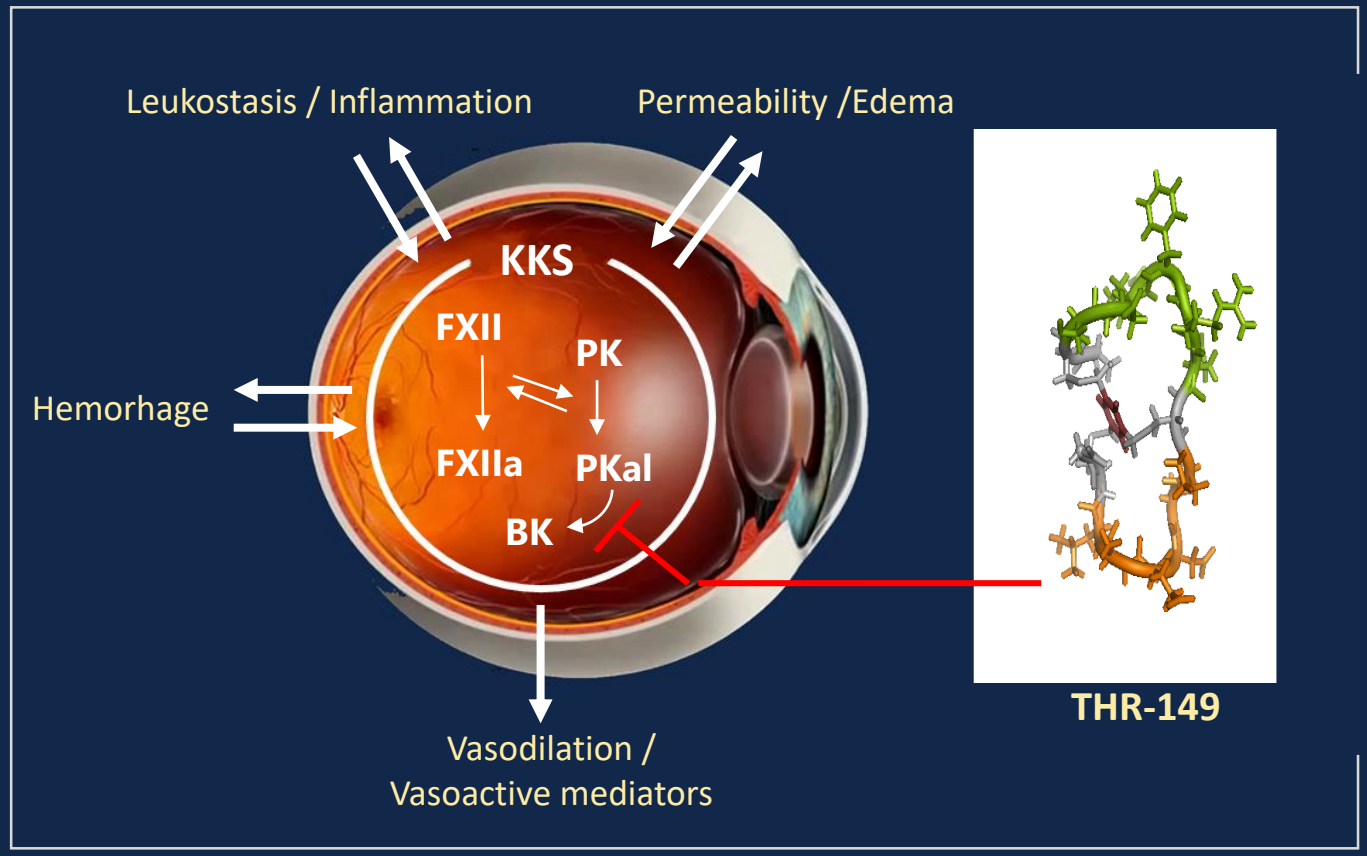
* For review: Campochiaro (2019) J. Clin. Invest. 129: 3029-31
Usui & Friedlander (2019) J. Clin. Invest. 129: 3032-34

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

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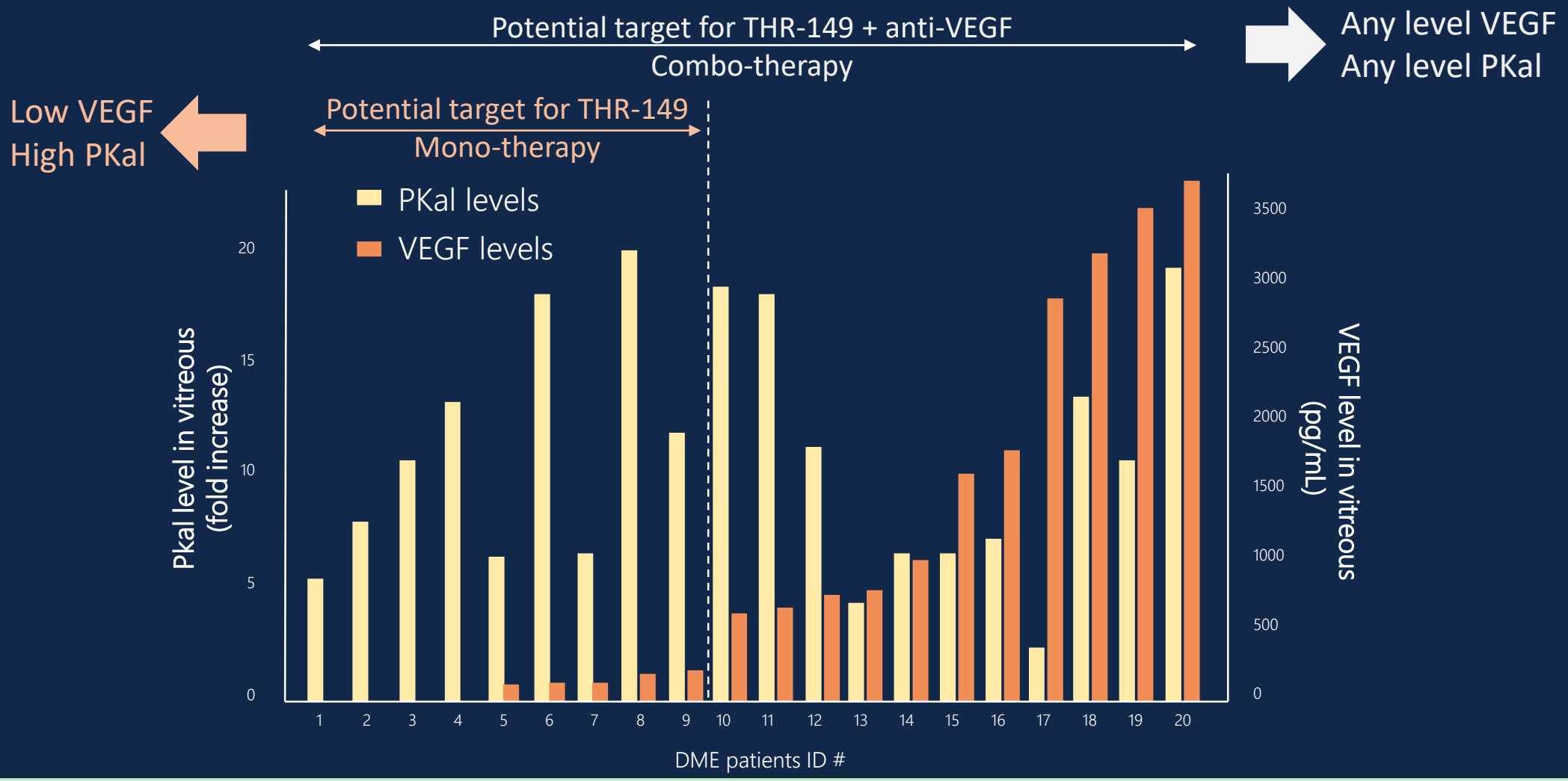
Rationale for Targeting PKal in DME



Start building clinical evidence with THR-149 mono-therapy

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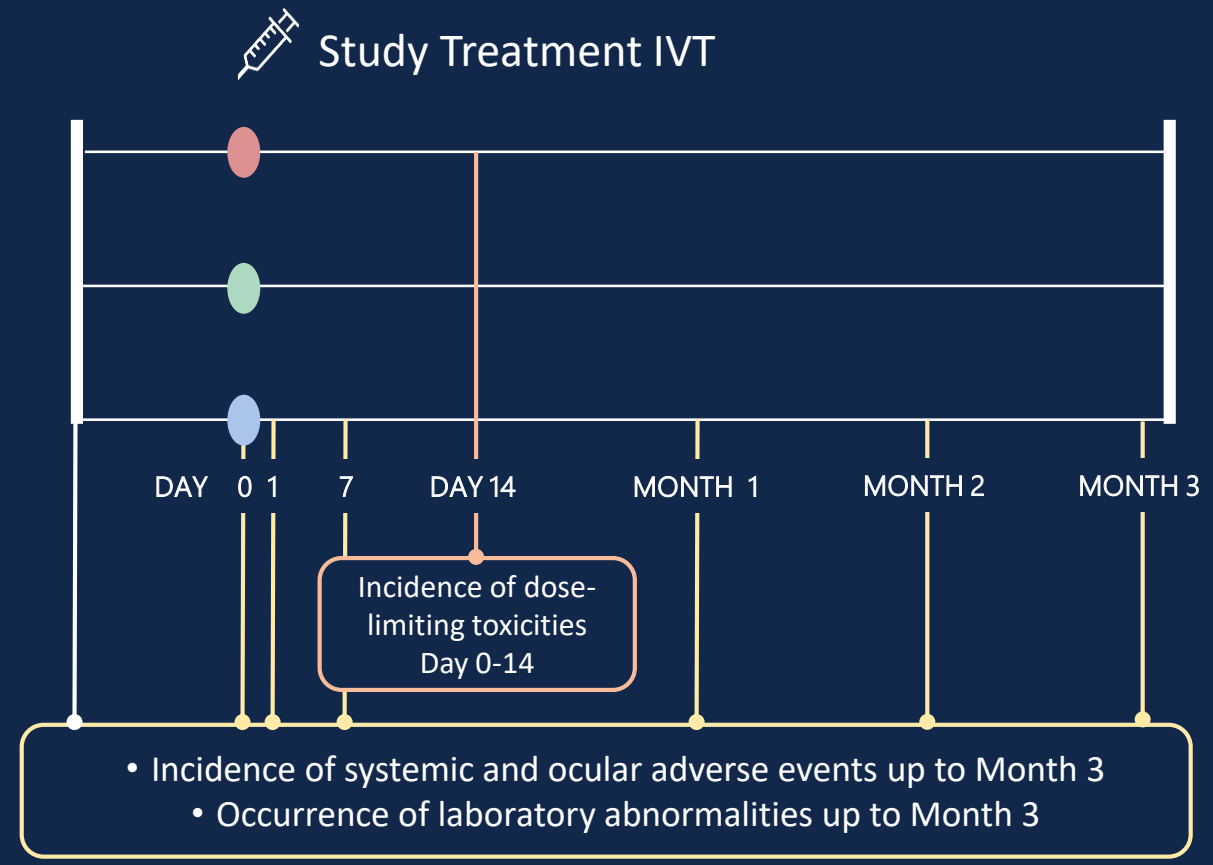
Adapted: Kita *et al.* 2015 Diabetes 64:3588–99

THR-149-001: Study Overview

3+3 Dose-Escalation Study

Total N = 12 patients

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



- 0.005mg THR-149 (low dose)
- 0.022mg THR-149 (middle dose)
- 0.13mg THR-149 (high dose)

- Screening
- Primary outcome measure
- Secondary outcome measures

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THR-149-001: Baseline Ocular Characteristics in the Study Eye

All Treated Subjects

Characteristic	Low Dose N=3	Middle Dose N=3	High Dose N=6
BCVA (ETDRS letters)			
Mean (SD)	46.0 (9.17)	46.7 (8.62)	43.0 (12.59)
Median	44.0	45.0	43.5
Min, Max	38, 56	39, 56	25, 58
CST (µm)			
Mean (SD)	497.7 (70.04)	539.3 (35.95)	529.5 (120.60)
Median	533.0	551.0	585.0
Min, Max	417, 543	499, 568	373, 626

No relevant imbalances between treatment arms for Baseline BCVA and CST

THR-149-001: Safety Overview

All Treated Subjects

Category	Low Dose N=3	Middle Dose N=3	High Dose N=6
	Number of events	Number of events	Number of events
Death	0	0	0
SAE	0	3	0
DLT	0	0	0
AE leading to withdrawal from study	0	0	0
Treatment-related (drug and / or procedure) AE	0	1	0

- 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

Adverse event	Low Dose N=3	Middle Dose N=3	High Dose N=6
	Number of events	Number of events	Number of events
Anterior chamber inflammation	0	1 [a]	0
Conjunctival hemorrhage	0	1	0
Corneal disorder	0	1	0
Diabetic retinal edema	1	1	1
Eye pain	0	0	1
Macular fibrosis [b]	0	2	0
Vitreous floaters	1	0	0

- 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

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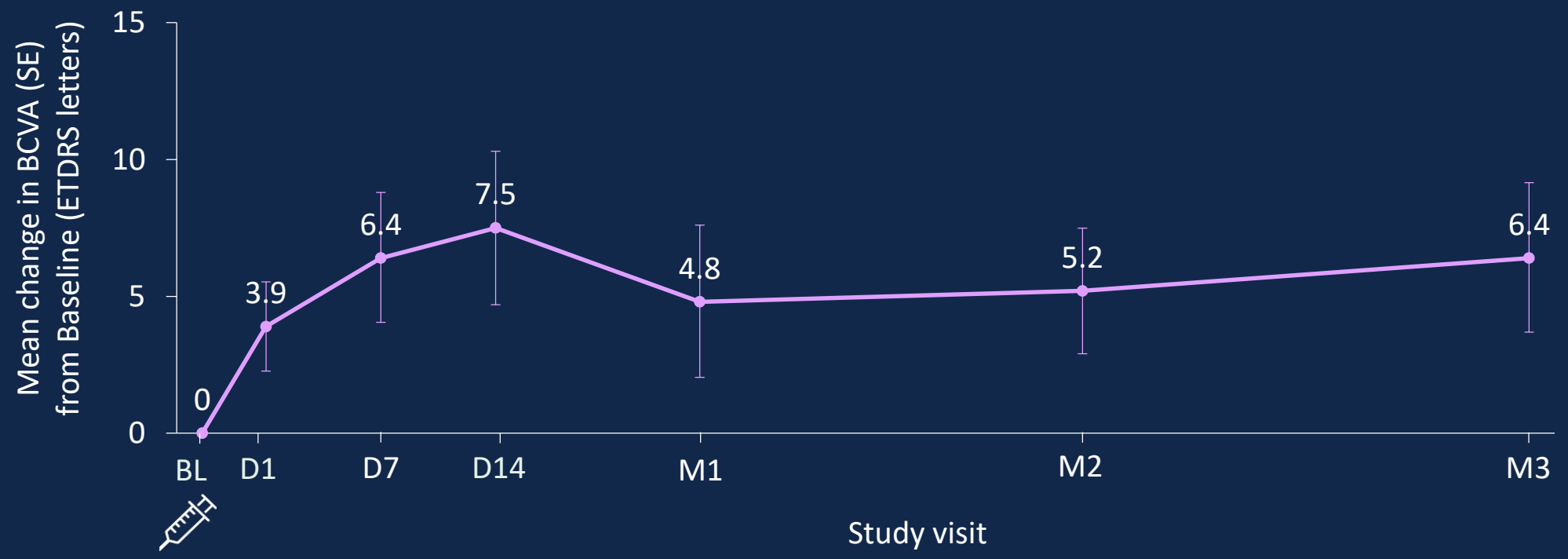
[a] Deemed treatment-related (drug and/or procedure) by the Investigator
[b] Epiretinal membrane (2 events in 1 subject)

THR-149-001: Mean Change in BCVA From Baseline (Accounted for Rescue)[a]

All Treated Subjects, Overall



Mean BCVA gain was fast and maintained until end of study

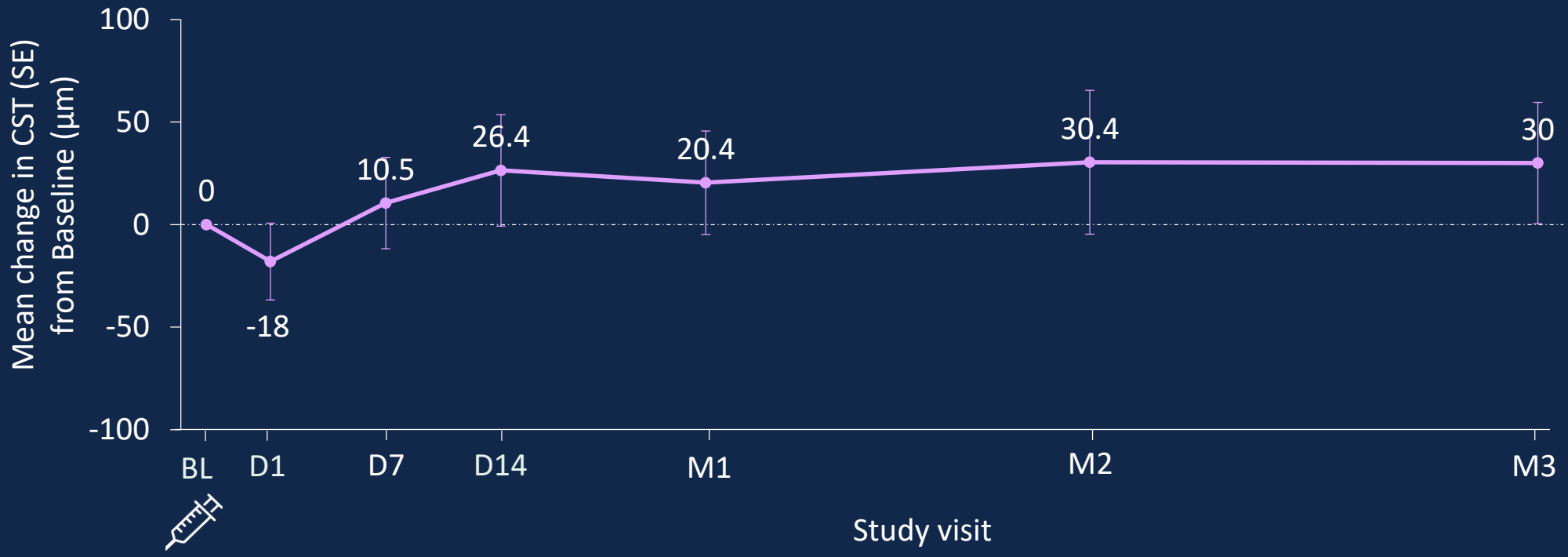
BL, Baseline; D, Day; M, Month; SE, standard error

[a]Value before rescue carried forward

Overall mean BCVA at Baseline was 44.7 ETDRS letters

THR-149-001: Mean Change in CST From Baseline (Accounted for Rescue)[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

BL, Baseline; D, Day; M, Month

[a]Value before rescue carried forward

Overall mean CST at Baseline was 524µm

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

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