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[1]

- RGD: $\alpha_V\beta_3$, $\alpha_V\beta_5$, α_V , $\alpha_5\beta_1$

INFLAMMATION[3]

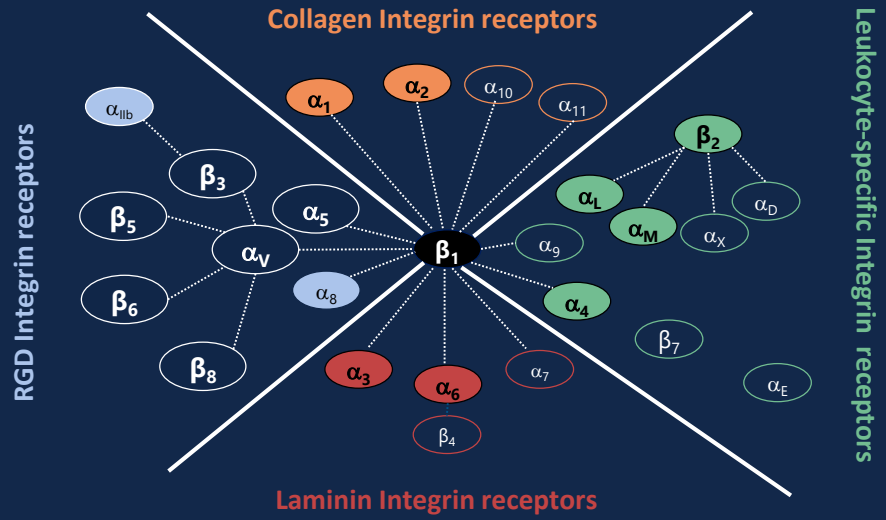
- RGD: $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_5\beta_1$
- Leukocyte: $\alpha_4\beta_{1(-7)}$, $\alpha_L\beta_2$, $\alpha_M\beta_2$
- Laminin: $\alpha_3\beta_1$

FIBROSIS[4]

- 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: $\alpha_6\beta_1$, $\alpha_3\beta_1$

PERMEABILITY[2]

- RGD: $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_5\beta_1$
- Leukocyte: $\alpha_4\beta_{1(-7)}$, $\alpha_L\beta_2$, β_2
- Laminin: $\alpha_3\beta_1$

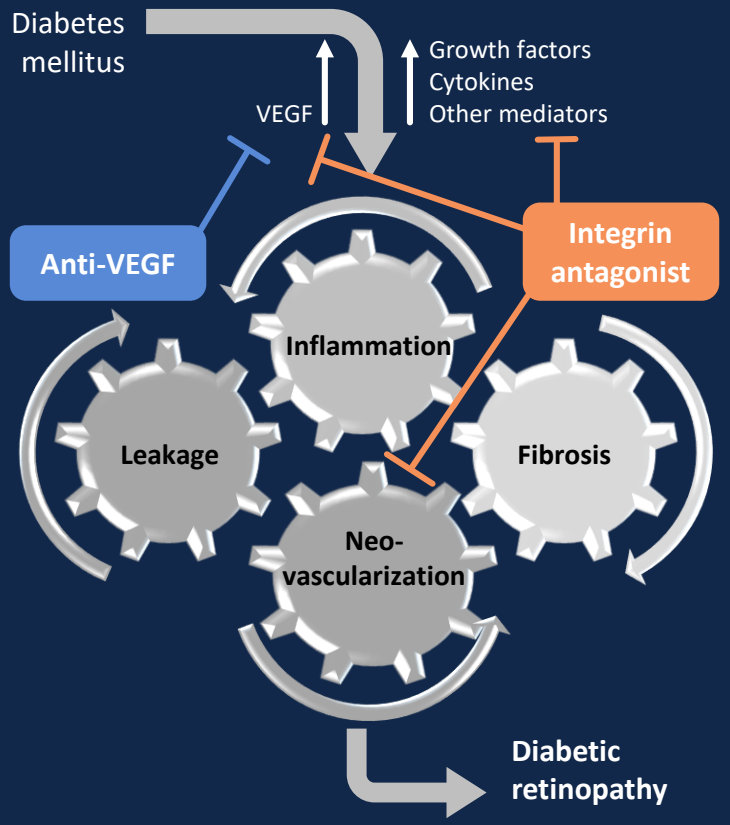


[1] Friedlander et al., 1996; Hammes et al., 1996; Umeda et al., 2006; Wilkinson-Berka et al., 2006; Fu et al., 2007; Santulli et al., 2008
[2] Joussen et al., 2004; Santulli et al., 2008; Iliaki et al., 2009; Lima e Silva et al., 2009; Rao et al., 2010; Hakanpaa et al., 2014; Park et al., 2014
[3] Joussen 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; Blanco-Mezquita et al., 2011; Lipson et al., 2012; Wang et al., 2012)

Abbreviation(s): RGD, arginylglycylaspartic acid

THR-687: A Pan-RGD Integrin Antagonist

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



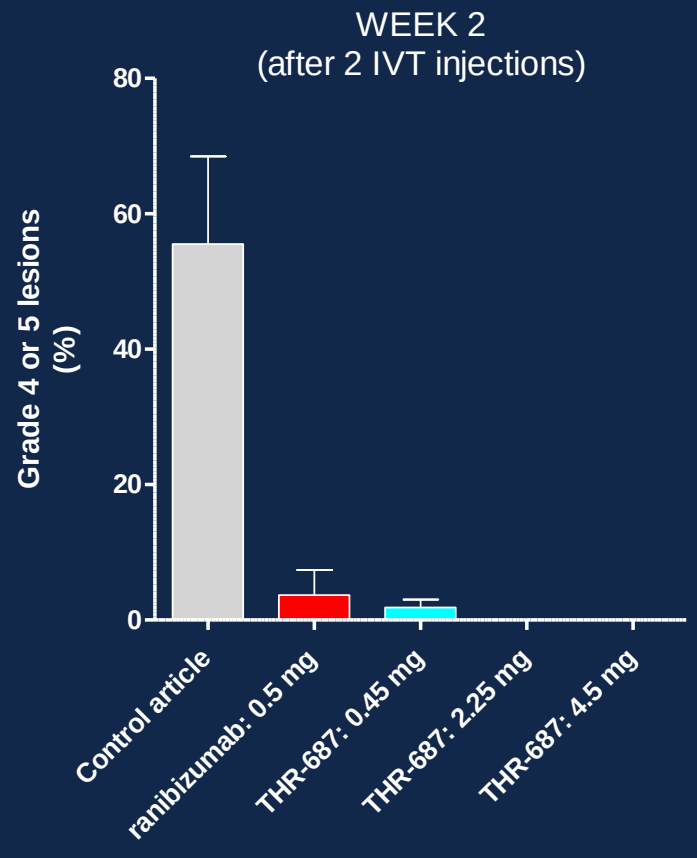
- THR-687 is a novel, potent RGD integrin antagonist[1]
- Inhibition of integrins targets multiple processes involved in pathological angiogenesis and vascular leakage
- THR-687 has a broad therapeutic potential:
  - Diabetic retinopathy (DR) with and without diabetic macular edema (DME)
  - Wet (neovascular)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

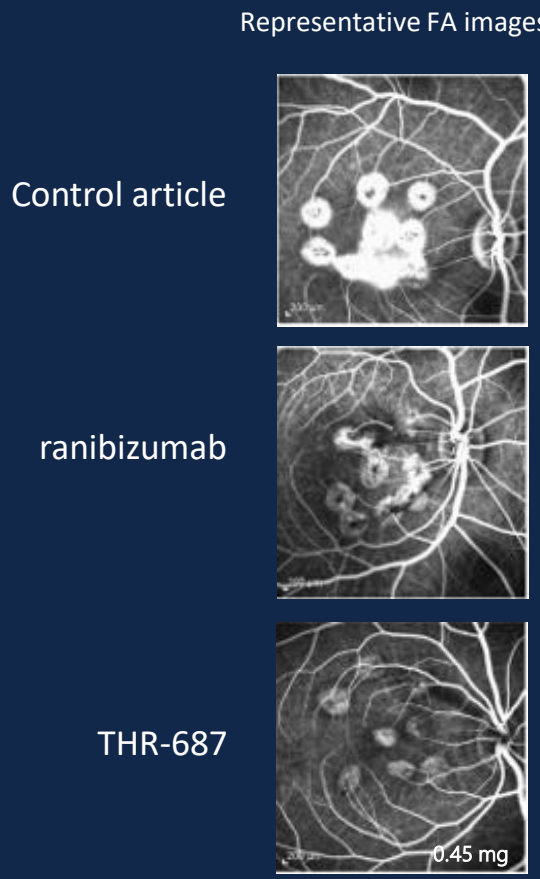
1. Hu TT et al. Exp Eye Res 2019;180:43-52

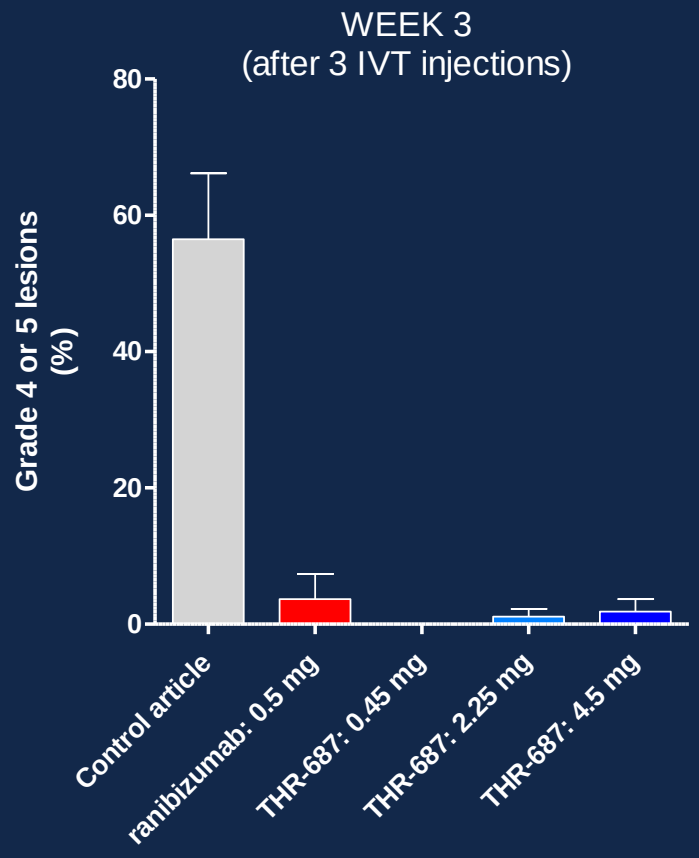
RGD, arginylglycylaspartic acid; VEGF, vascular endothelial growth factor

THR-687: Anti-angiogenic effect

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







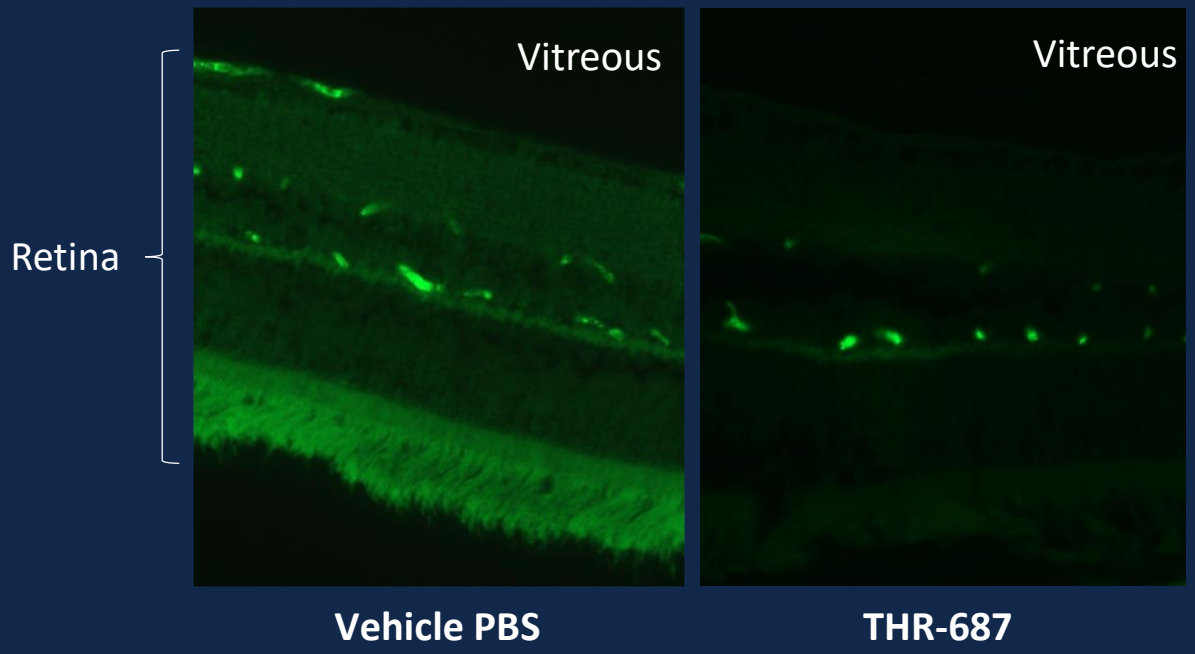
Hu TT et al. Exp Eye Res 2019;180:43-52

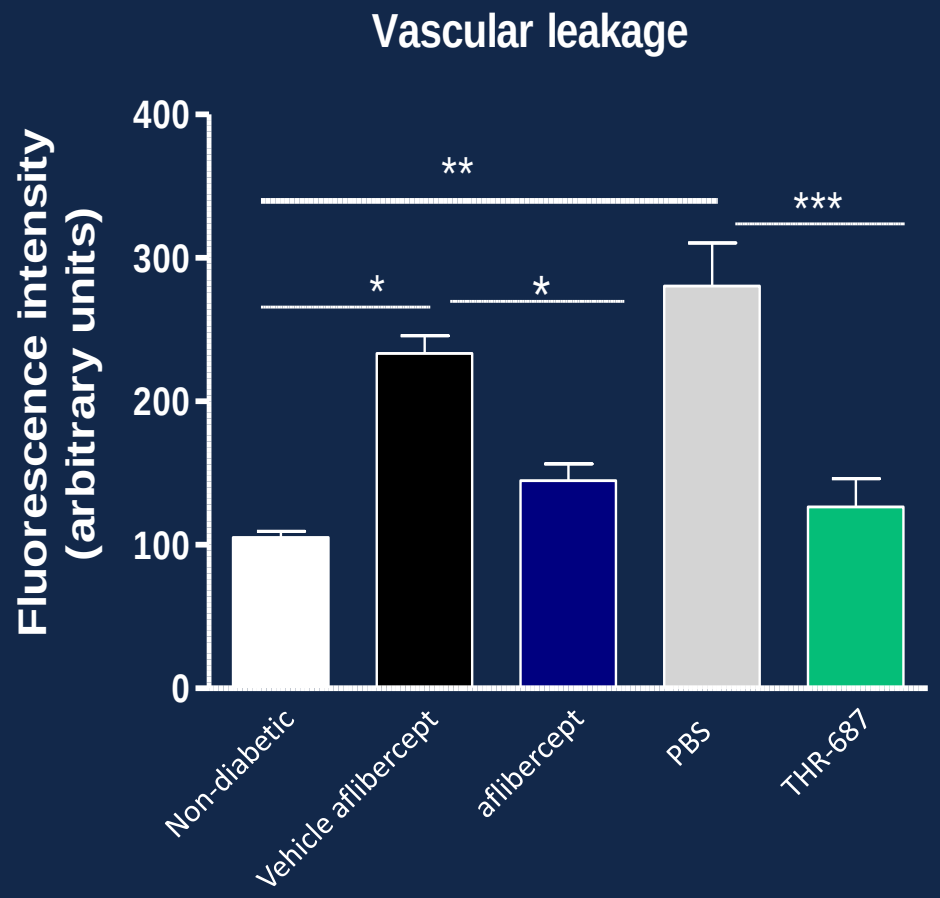
Abbreviation(s): CNV, choroidal neovascularization; IVT, intravitreal

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





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

Hu TT et al., 2019, EVER Abstract Number: 5063; F.094

Abbreviation(s): FITC-BSA, Fluorescein isothiocyanate labelled bovine serum albumin; STZ, streptozotocin

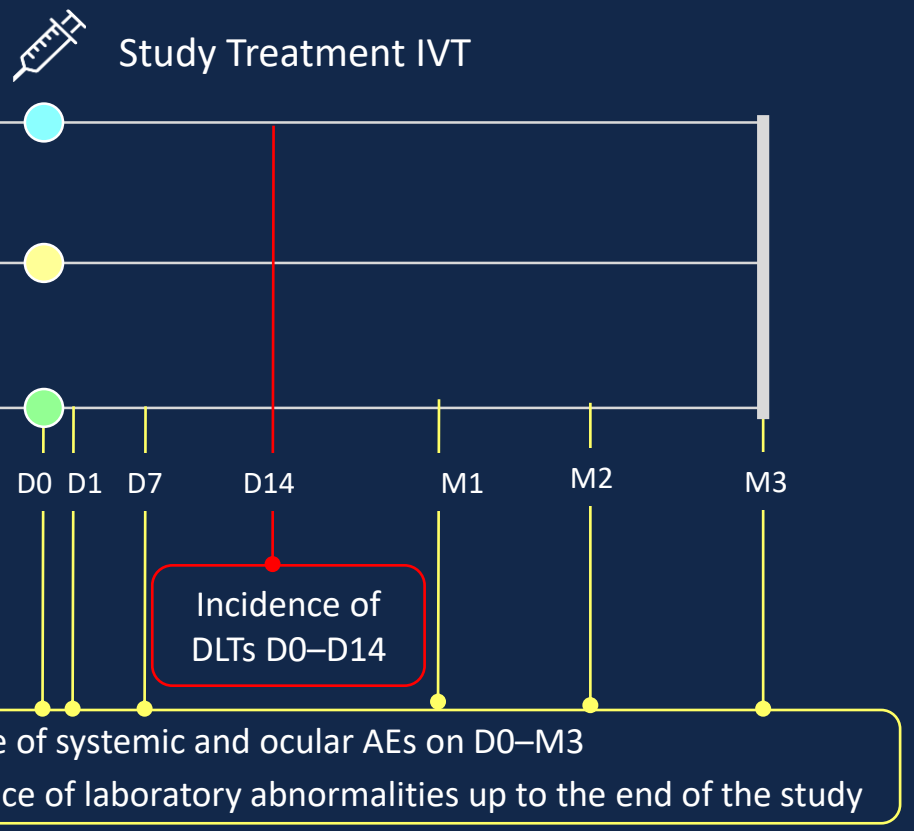
Hu TT et al. Poster Presented at EVER 2019, Nice, France.

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

- 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;
* Spectralis SD-OCT, spectral domain optical coherence tomography

THR-687-001: Demographics

All Treated Subjects

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

- Most subjects were male and white.
- Average age was 57.8 years and there were no relevant differences between the dose groups.

SD, standard deviation

THR-687-001: Baseline Ocular Characteristics in the Study Eye (1/2)

All Treated Subjects

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

- There was no relevant imbalance between the groups for BCVA
- CST was lower in the high dose group compared to the other dose groups.

Baseline defined as Day 0 for BCVA, Day 1 for CST

THR-687-001: Baseline Ocular Characteristics in the Study Eye (2/2)

All Treated Subjects

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

- 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

Category	Low Dose N=3	Middle Dose N=3	High Dose N=6	Overall N=12	
	n [E]	n [E]	n [E]	n (%)	E
Death	0	0	0	0	0
SAE	0	0	0	0	0
DLT	0	0	0	0	0
AE leading to withdrawal from study	0	0	0	0	0
Treatment-related (drug and / or procedure) AE – all in Study Eye, non-severe	1 [2]	1 [1]	1 [1]	3 (25.0)	4

- No DLTs occurred at any dose
- No SAEs developed
- There was one subject in each dose group with a treatment-related AE(s)

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

THR-687-001: Adverse Events in the Study Eye

All Treated Subjects

Adverse event	Low Dose N=3	Middle Dose N=3	High Dose N=6	Overall N=12	
	n [E]	n [E]	n [E]	n (%)	E
	1 subjects, 2 events	1 subjects, 3 events	3 subjects, 4 events	5 subjects, 9 events	
Diabetic retinal edema	0	1 [1]	2 [2]	3 (25.0)	3
Conjunctival hemorrhage	1 [1] [a]	1 [1] [a]	0	2 (16.7)	2
Eye pain	0	0	1 [1] [a]	1 (8.3)	1
Intraocular pressure increased	1 [1] [a]	0	0	1 (8.3)	1
Ocular hypertension	0	1 [1]	0	1 (8.3)	1
Vision blurred	0	0	1 [1]	1 (8.3)	1

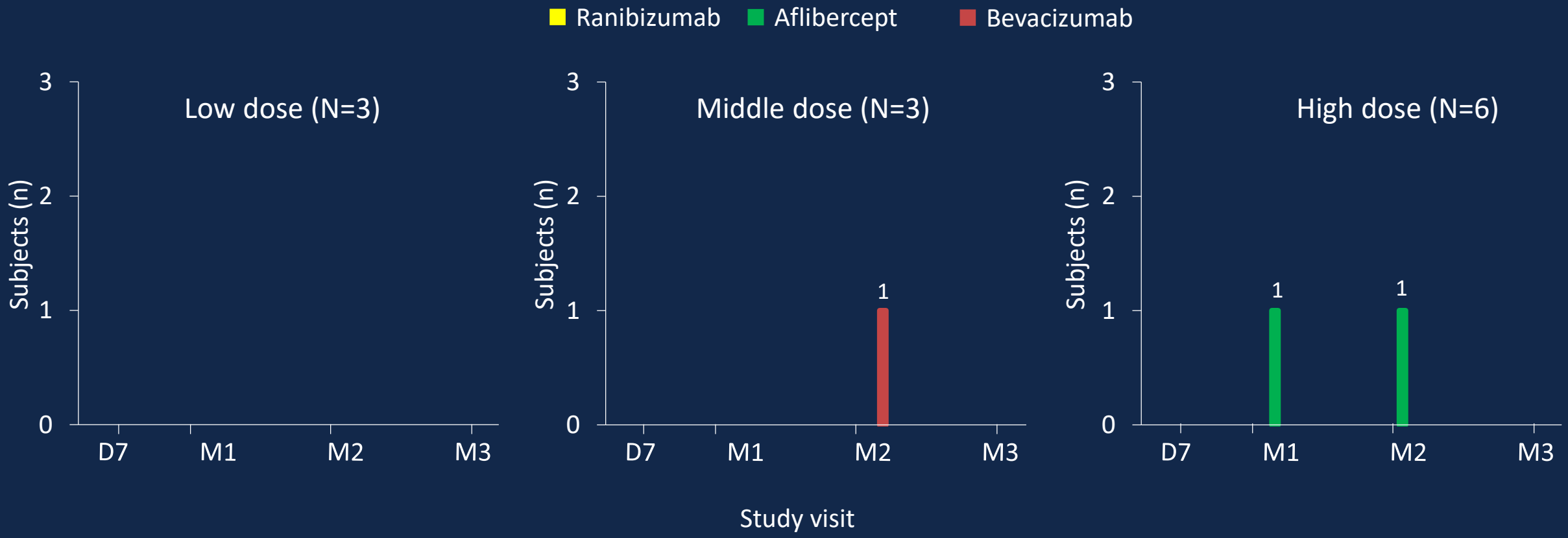
- All AEs deemed treatment-related by the Investigator, were ocular and likely injection procedure related
- Other AEs were likely due to the injection procedure, underlying disease progression, or concomitant diseases
- No cases of endophthalmitis or intraocular inflammation

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

THR-687-001: First Rescue Treatment

All Treated Subjects



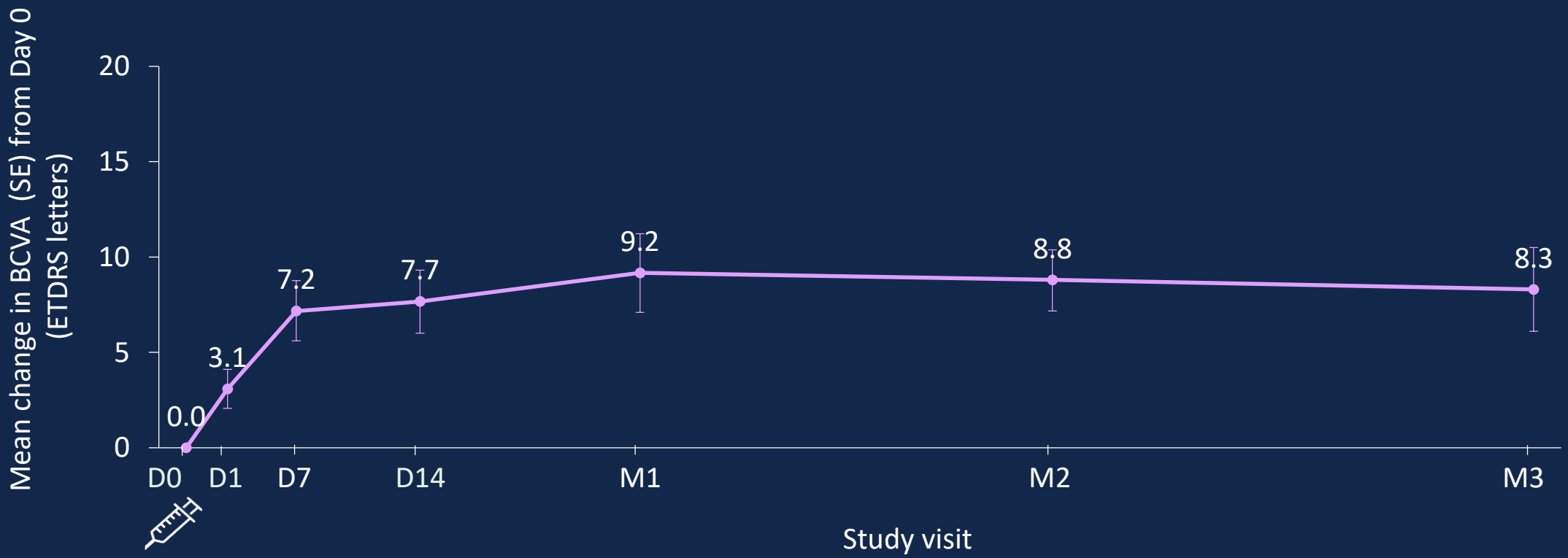
Rescue criteria:
Standard-of-care treatment for DME can be administered in the study eye if deemed necessary by the Investigator and if at least one of the following criteria is met:

- ≥ 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

D, Day; M, Month

THR-687-001: Mean Change in BCVA From Day 0 (Accounted for Rescue)[a]

All Treated Subjects, Overall

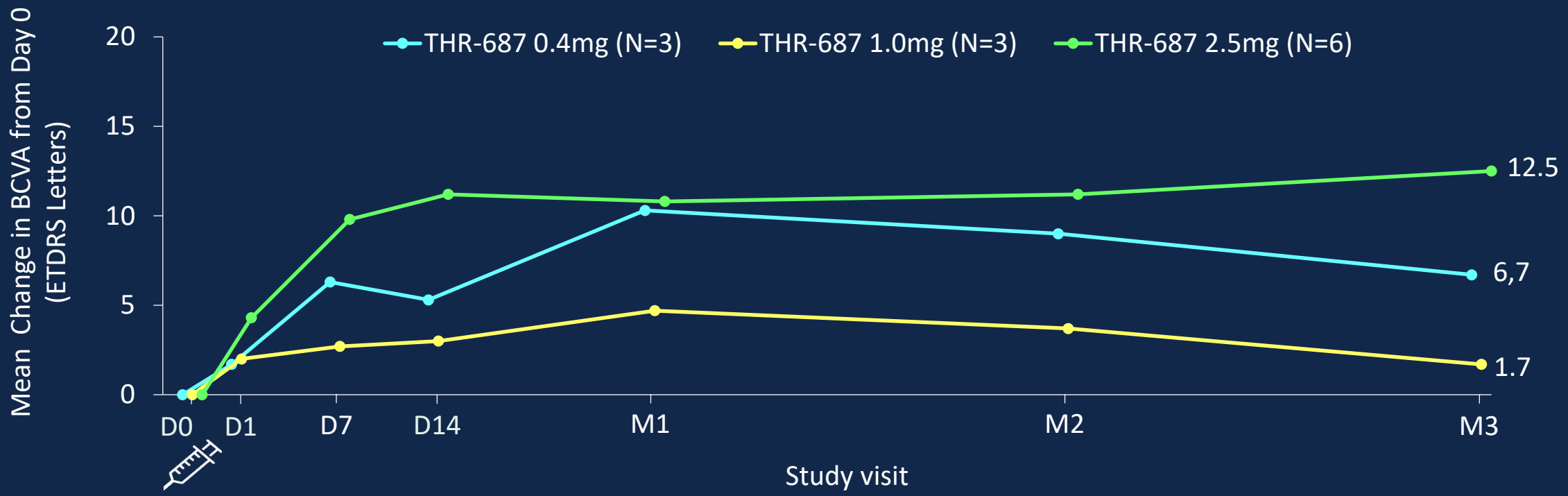


- A rapid onset of action in mean BCVA was observed as of Day 1 with 3.1 letters gain
- Mean BCVA gain was the highest at Month 1, with 9.2 letters
- Mean BCVA gain was maintained post-injection, with a mean gain of 8.3 letters at Month 3

[a]Value before rescue carried forward;
D, Day; M, Month; SE, standard error;

THR-687-001: Mean Change in BCVA From Day 0 (Accounted for Rescue)[a]

All Treated Subjects, By Dose

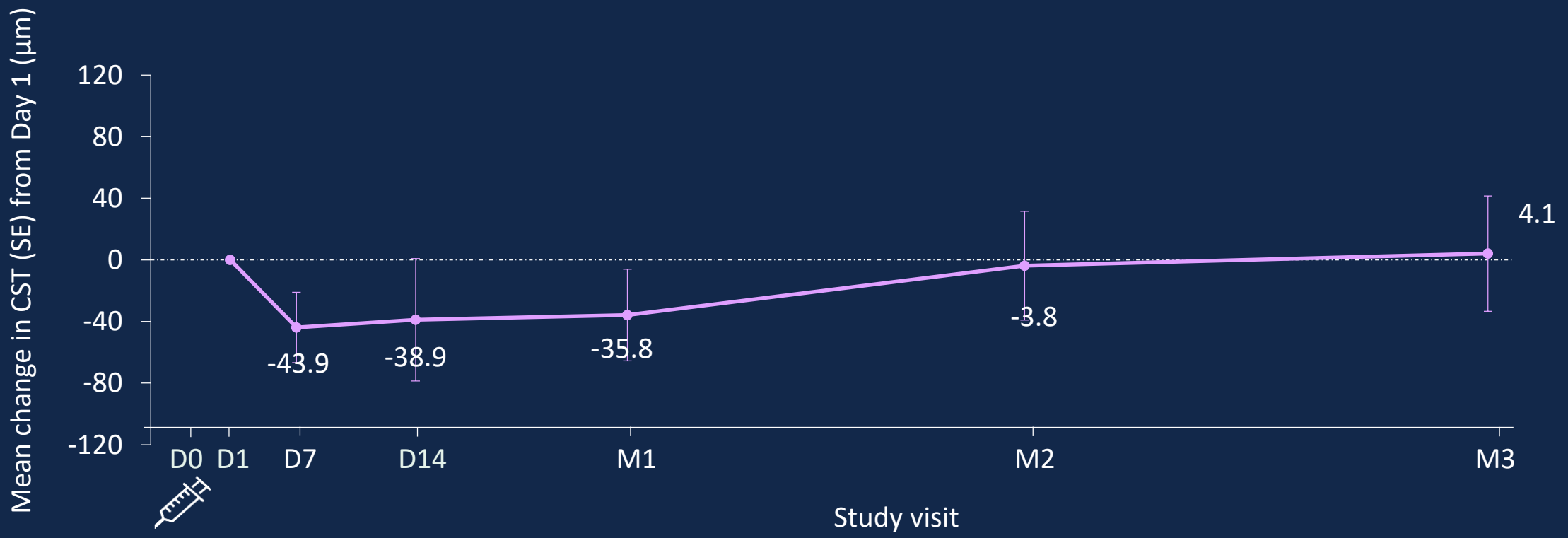


- BCVA improvement was most pronounced in the high dose group, with a mean BCVA gain of 12.5 letters at Month 3

[a]Value before rescue carried forward; D, Day; M, Month;

THR-687-001: Mean Change in CST From Day 1 (Accounted for Rescue)[a]

All Treated Subjects, Overall

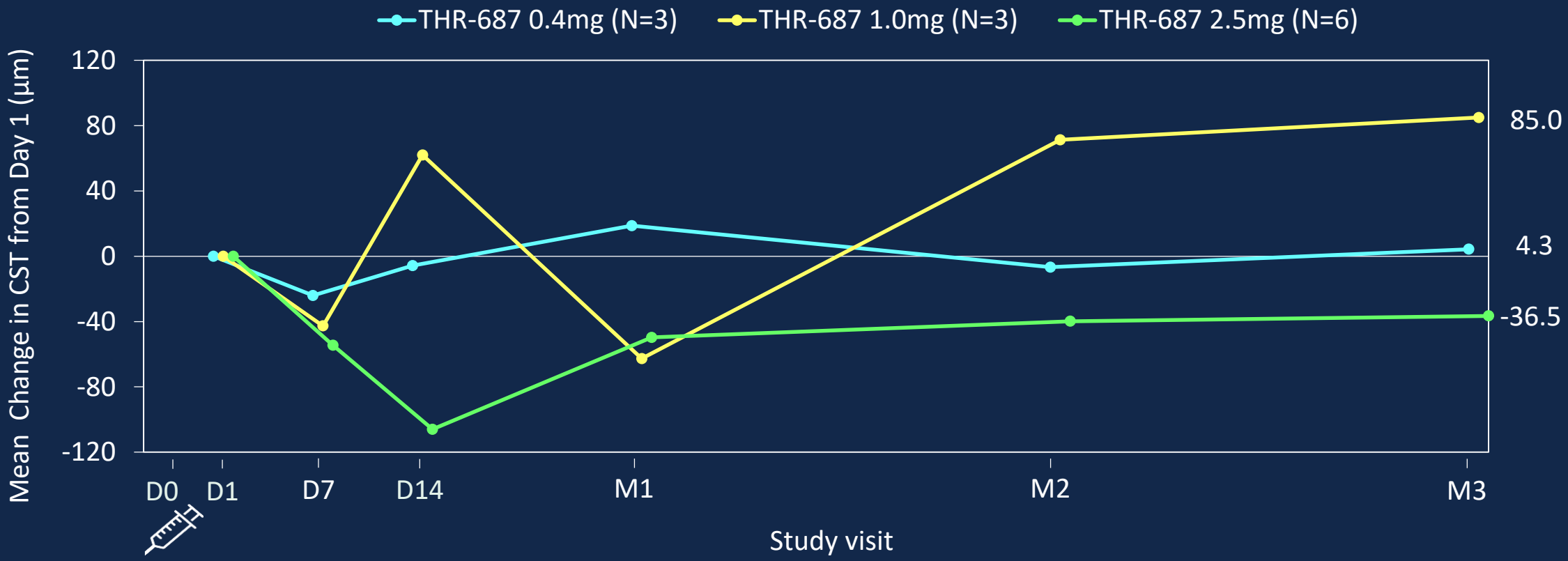


- Overall, marginal impact on mean CST was noted up to Month 1, followed by a return to baseline level until Month 3

SD-OCT not assessed at Day 0; [a]Value before rescue carried forward;
D, Day; M, Month; SE, standard error;

THR-687-001: Mean Change in CST From Day 1 (Accounted for Rescue)[a]

All Treated Subjects, By Dose

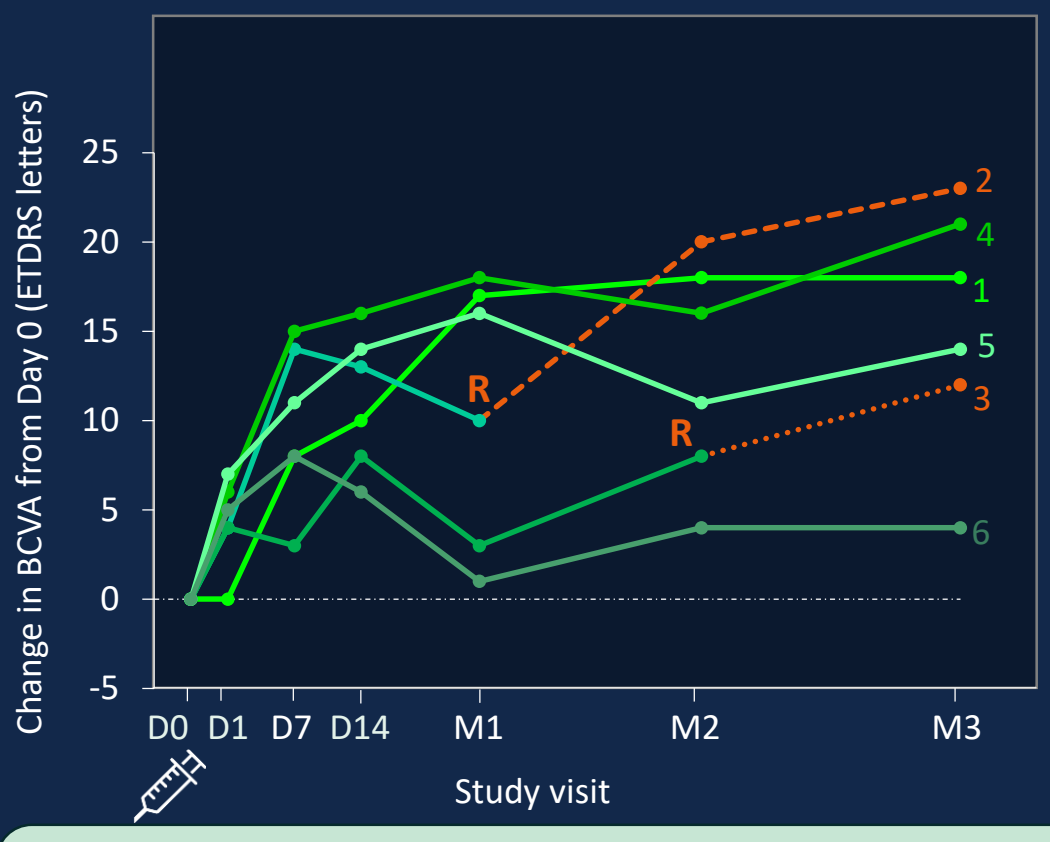


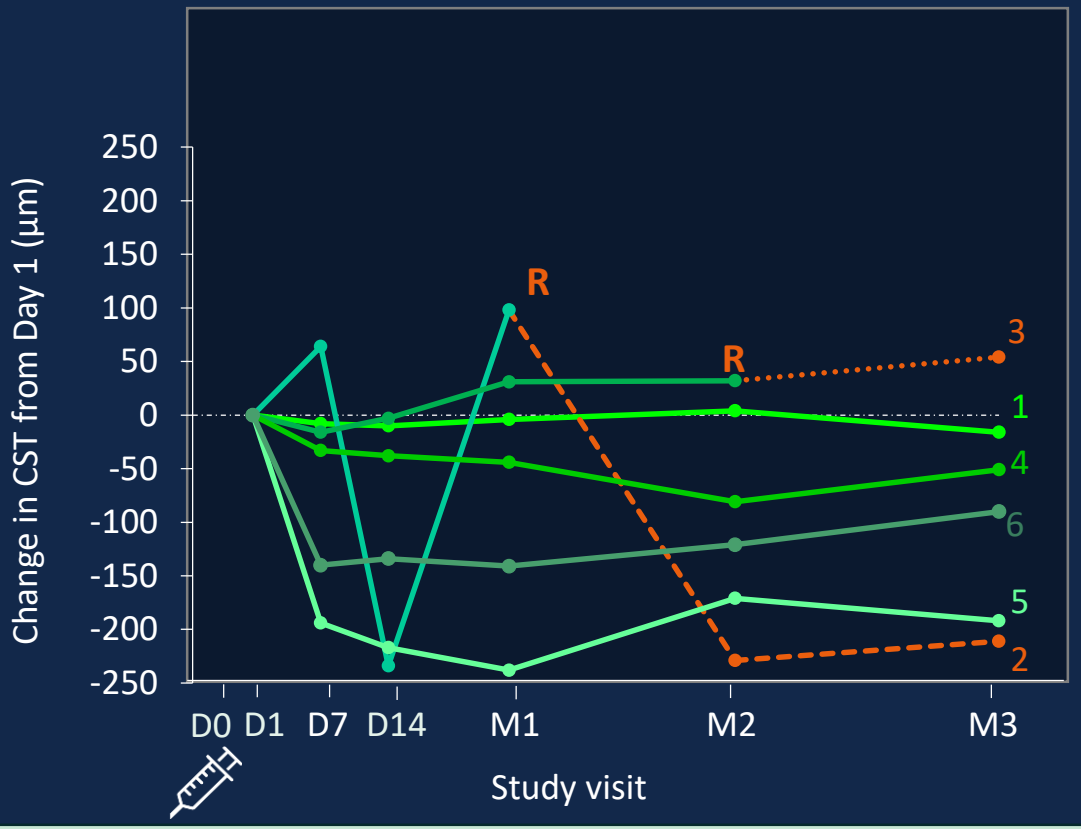
- A pronounced mean decrease in CST was noted in the high dose, with a decrease of 106 µm at Day 14

SD-OCT not assessed at Day 0; [a]Value before rescue carried forward;
D, Day; M, Month;

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

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