THR-317-001: Safety and Efficacy of THR-317 for the Treatment of Diabetic Macular Edema

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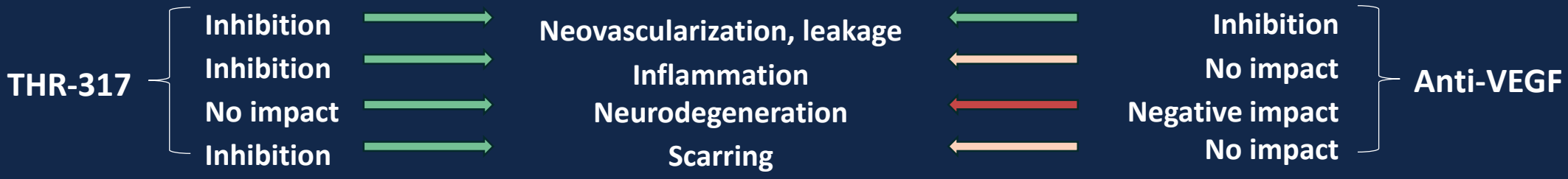
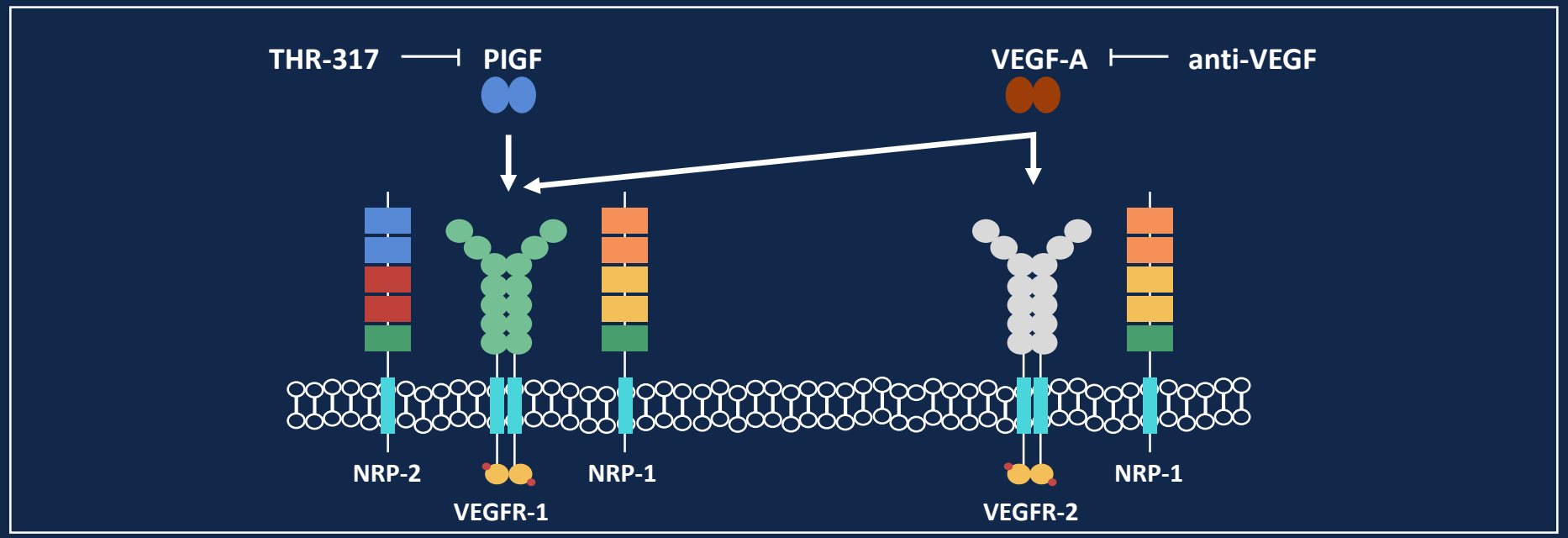
THR-317: A Humanized mAb Against Human PlGF[1,2]

- Anti PLFG reduces NV & leakage in a mouse model of CNV, comparable to VEGF inhibition
- Additional benefits may be activation of protective factors decreasing inflammation and pericyte loss with preservation of the BRB as well as inhibition of fibrosis





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1. Van Bergen et al. 2018 Prog. Retin. Eye Res. Published online 30 October.
2. Van Bergen T, et al. Exp Eye Res. 2017;165:136–50.

THR-317-001: Two-Stage Study Design

Primary endpoint: Incidence of acute (up to the Day 7 post-injection visit) ocular (serious) adverse events in the study eye, after each injection and across injections per subject

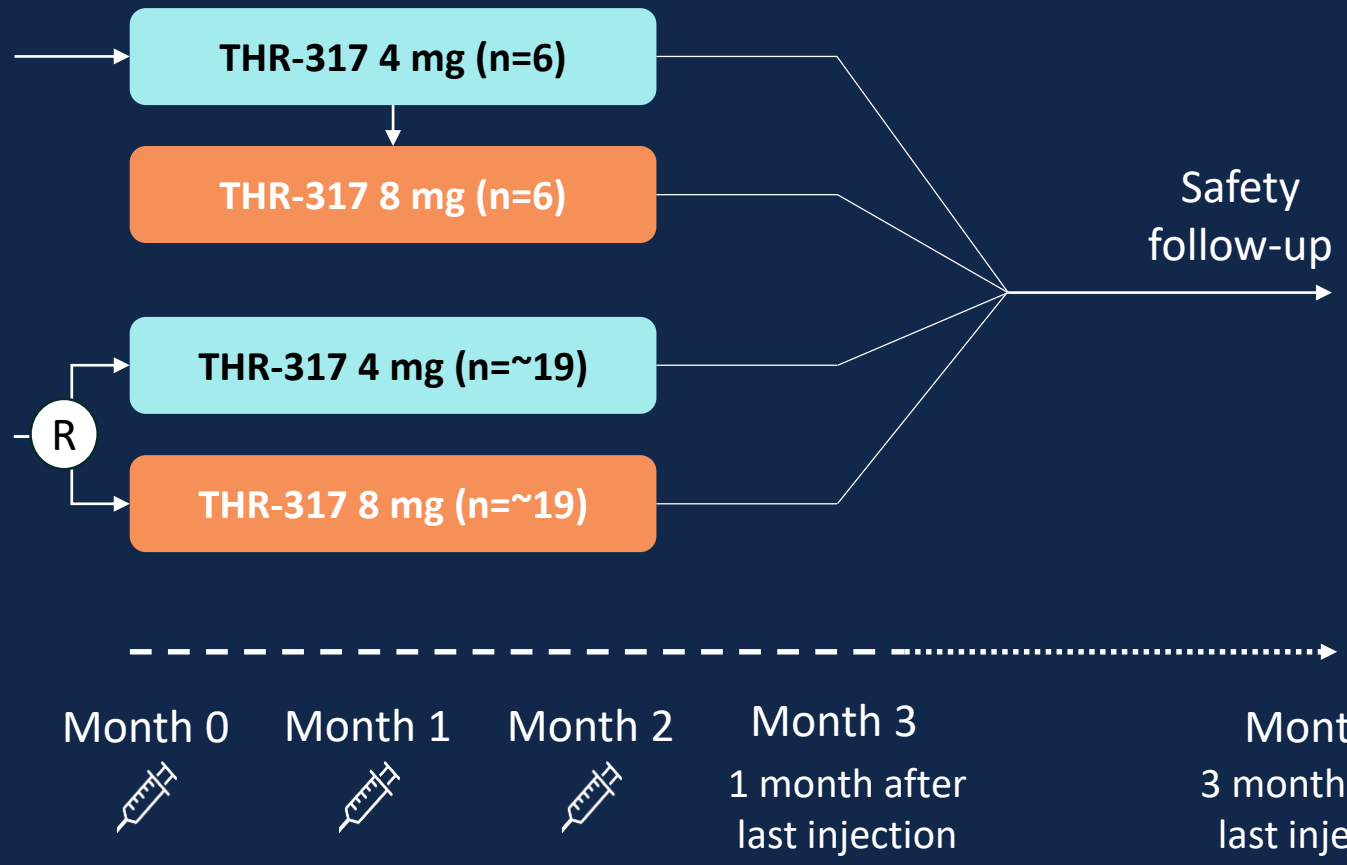
Treatment population

- **Adults with center-involved DME (N=~50)**

Strata

- **Anti-VEGF treatment naïve (n=~40)**
- **Anti-VEGF poor responders (n=~10)**

- **BCVA between 72 and 23 ETDRS letter score (20/40 and 20/320 Snellen equivalent) in study eye**



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THR-317-001: Key Inclusion/Exclusion Criteria (study eye)

Inclusion

- Center-involved DME with CST ≥340 µm on Spectralis SD-OCT or ≥320 µm on non-Spectralis SD-OCT assessed by reading center
- BCVA ETDRS letter score between 72 and 23 letters (20/40 and 20/320 Snellen equivalent)
- NPDR or stable PDR
- Anti-VEGF treatment naïve or poor response to prior anti-VEGF treatment

Exclusion

- Macular edema due to causes other than DME
- Aphakia
- Uncontrolled glaucoma (IOP ≥26 mmHg despite treatment with antiglaucoma medication)
- HbA1c >12%

- Poor response to prior anti-VEGF treatment was defined as no or limited response despite previous treatment with at least 3 consecutive anti-VEGF injections given in the year prior to Screening, resulting in <5 ETDRS letters increase in BCVA from Baseline and/or <10% reduction in CST from Baseline

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THR-317-001: Demographics

All Treated Subjects, by Prior Anti-VEGF Treatment Status

Characteristic	THR-317 4 mg			THR-317 8 mg		
	Anti-VEGF treatment naïve N=20	Anti-VEGF poor responder N=4	Overall N=24	Anti-VEGF treatment naïve N=20	Anti-VEGF poor responder N=5	Overall N=25
Gender, n (%)						
Male	9 (45.0)	3 (75.0)	**12 (50.0)**	10 (50.0)	1 (20.0)	**11 (44.0)**
Female	11 (55.0)	1 (25.0)	**12 (50.0)**	10 (50.0)	4 (80.0)	**14 (56.0)**
Race, n (%)						
White	20 (100.0)	4 (100.0)	**24 (100.0)**	20 (100.0)	5 (100.0)	**25 (100.0)**
Age (years)						
Mean (SD)	63.9 (8.26)	57.3 (7.76)	**62.8 (8.40)**	64.7 (8.77)	70.6 (6.58)	**65.8 (8.61)**
Min, max	38, 81	51, 67	**38, 81**	44, 81	63, 78	**44, 81**

- **No apparent imbalances between treatment arms and within the 2 strata (anti-VEGF treatment naïve subjects and anti-VEGF treatment poor responders)**

THR-317-001: Baseline BCVA and CST in the Study Eye

All Treated Subjects, by Prior Anti-VEGF Treatment Status

Characteristic	THR-317 4 mg			THR-317 8 mg		
	Anti-VEGF treatment naïve N=20	Anti-VEGF poor responder N=4	Overall N=24	Anti-VEGF treatment naïve N=20	Anti-VEGF poor responder N=5	Overall N=25
BCVA (ETDRS letters)						
Mean (SD)	67.3 (5.27)	60.5 (9.81)	**66.1 (6.49)**	62.6 (8.74)	61.4 (4.10)	**62.3 (7.97)**
Min, Max	56, 72	46, 67	**46, 72**	36, 72	58, 68	**36, 72**
BCVA, categorical, n (%)						
≤65 Letters	7 (35.0)	2 (50.0)	**9 (37.5)**	11 (55.0)	4 (80.0)	**15 (60.0)**
>65 Letters	13 (65.0)	2 (50.0)	**15 (62.5)**	9 (45.0)	1 (20.0)	**10 (40.0)**
CST (µm)						
Mean (SD)	435.1 (102.01)	663.3 (232.71)	**473.1 (152.33)**	506.3 (78.87)	426.6 (90.81)	**490.3 (85.77)**
Median	397.5	707.0	**406.5**	503.0	377.0	**497.0**

- **Overall, BCVA tended to be higher in the 4 mg arm**
- **Strata:**
  - **Anti-VEGF treatment naïve: BCVA tended to be higher and mean CST lower in the 4 mg arm**
  - **Poor responders: Mean CST higher in the 4 mg arm - due to 2 outliers (836 µm and 866 µm)**

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THR-317-001: Safety Overview

All Treated Subjects

Category	THR-317 4 mg N=24 n (%)	THR-317 8 mg N=25 n (%)
Deaths	0 (0.0)	0 (0.0)
SAE		
Any ocular SAE	0 (0.0)	0 (0.0)
Any nonocular SAE[a]	1 (4.2)	0 (0.0)
AE leading to withdrawal from study	0 (0.0)	0 (0.0)
AE leading to withdrawal from repeat injection	0 (0.0)	0 (0.0)
Arterial thromboembolic events	0 (0.0)	0 (0.0)

- **No safety signals observed in either treatment arm**
- **No arterial thromboembolic event in either treatment arm during the study**

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[a]Not deemed treatment-related (drug and/or procedure) by the Investigator

THR-317-001: Summary of Adverse Events (1/2)

All Treated Subjects

Category	THR-317 4 mg N=24	THR-317 8 mg N=25
	n (%)	n (%)
Overall		
Any AE	9 (37.5)	11 (44.0)
Any AE in study eye	5 (20.8)	7 (28.0)
Any AE in nonstudy eye	2 (8.3)	1 (4.0)
Any nonocular AE	6 (25.0)	5 (20.0)

- **Overall incidence of AEs similar between the 2 treatment arms**
- **No AEs led to withdrawal from the study or withdrawal from repeat injection**

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THR-317-001: Acute (Up to Day 7 PI) Adverse Events in the Study Eye

All Treated Subjects

Adverse event	THR-317 4 mg Across injections N=24	THR-317 8 mg Across injections N=25
	n (%)	n (%)
	3 subjects, 3 events	4 subjects, 4 events
Conjunctival hemorrhage	1 (4.2)	1[a] (4.0)
Ocular hyperemia	0 (0.0)	1[a] (4.0)
Conjunctivitis	0 (0.0)	1 (4.0)
Eye pain	0 (0.0)	1[a] (4.0)
Visual impairment	2[b] (8.3)	0 (0.0)

- Overall incidence of acute AEs in the study eye was low
- All acute AEs in the study eye were mild in severity
- No acute AEs in the study eye were SAEs
- All acute AEs in the study eye resolved within 1 to 31 days of onset

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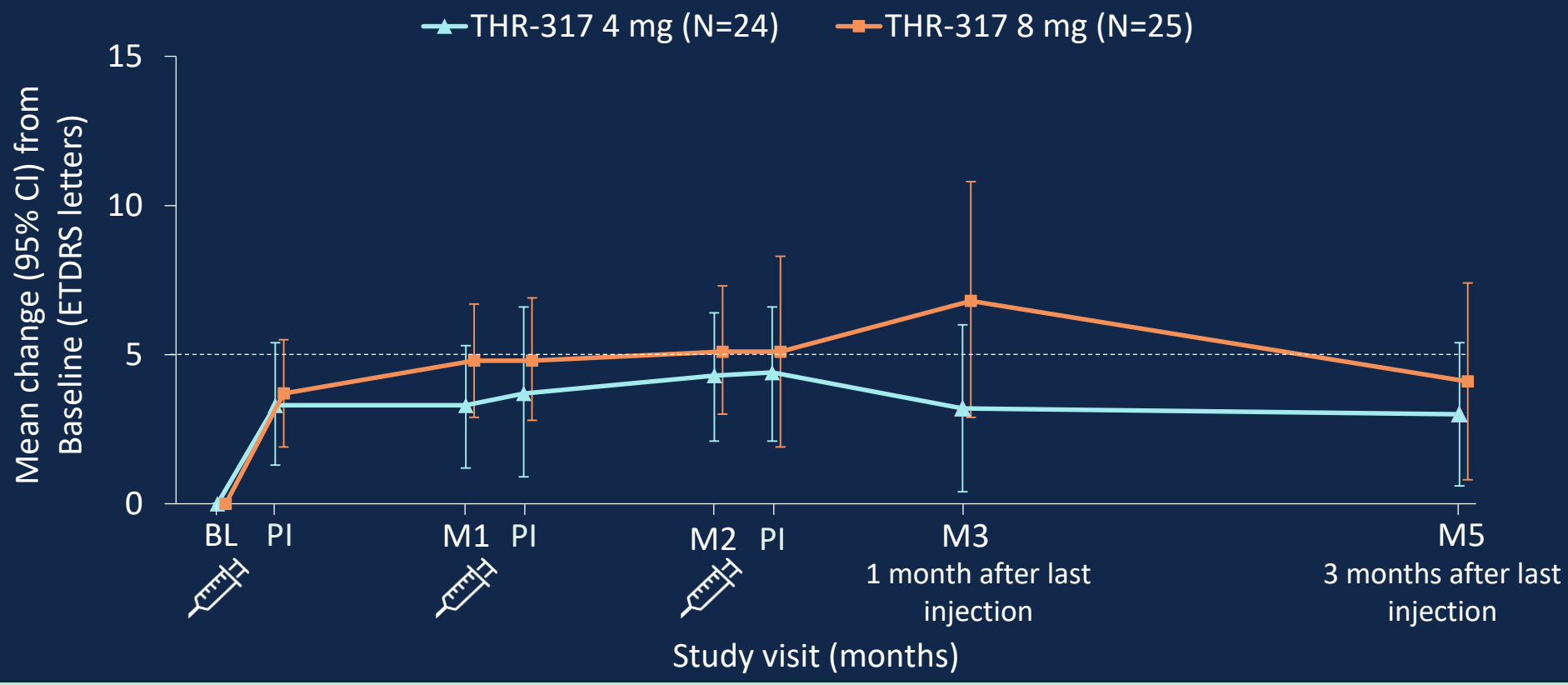
[a]AE was deemed treatment-related (drug and/or procedure) by the Investigator;
[b]Black spots in visual field. One of these AEs was deemed treatment-related (drug and/or procedure) by the Investigator

THR-317-001: Mean Change in BCVA From Baseline

All Treated Subjects



- **Increase in mean BCVA shortly after first injection in both treatment arms**
- **Increases in mean BCVA maintained to M5**
- **Trend for higher BCVA increases in the 8 mg arm**
- **Continued BCVA gain in the 8 mg arm, with highest increase at M3**

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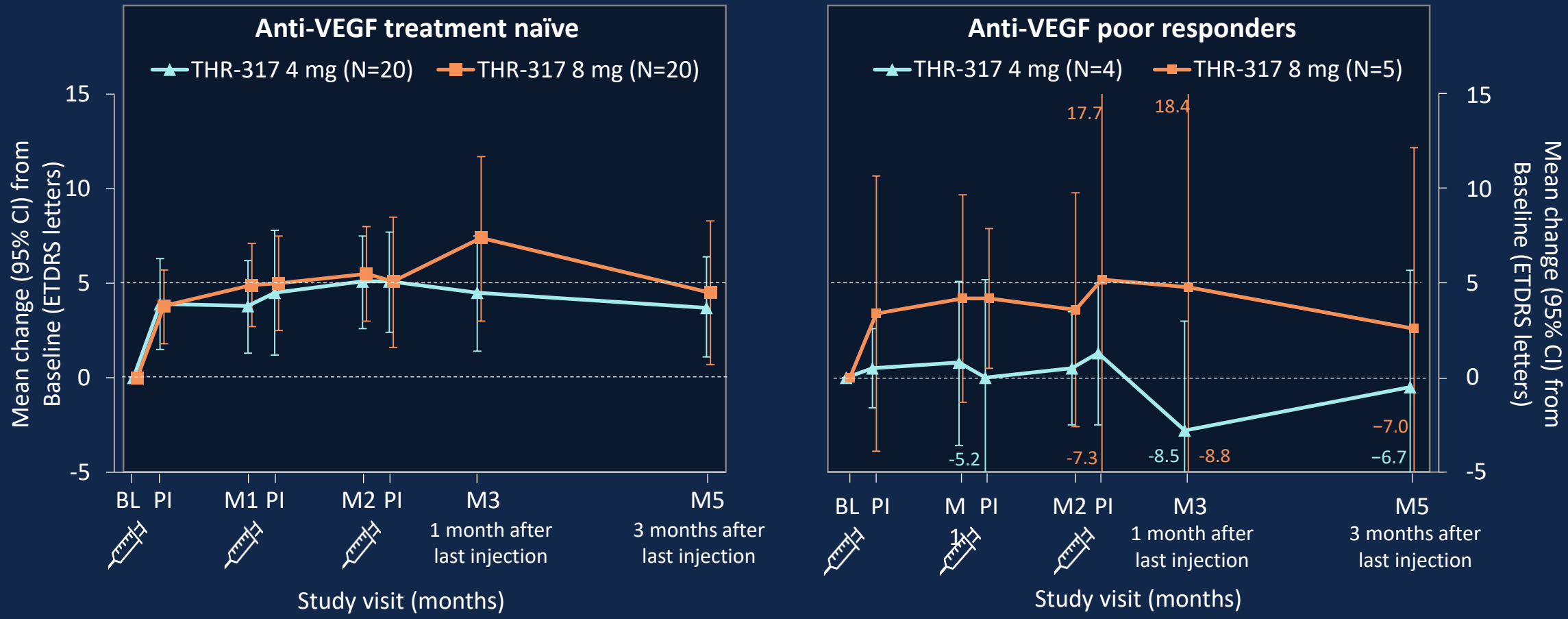
BL, Baseline; PI, post-injection visit (7 days after each injection)

THR-317-001: Mean Change in BCVA From Baseline



- **In both subgroups, there was a trend for higher BCVA increases in the 8 mg arm**

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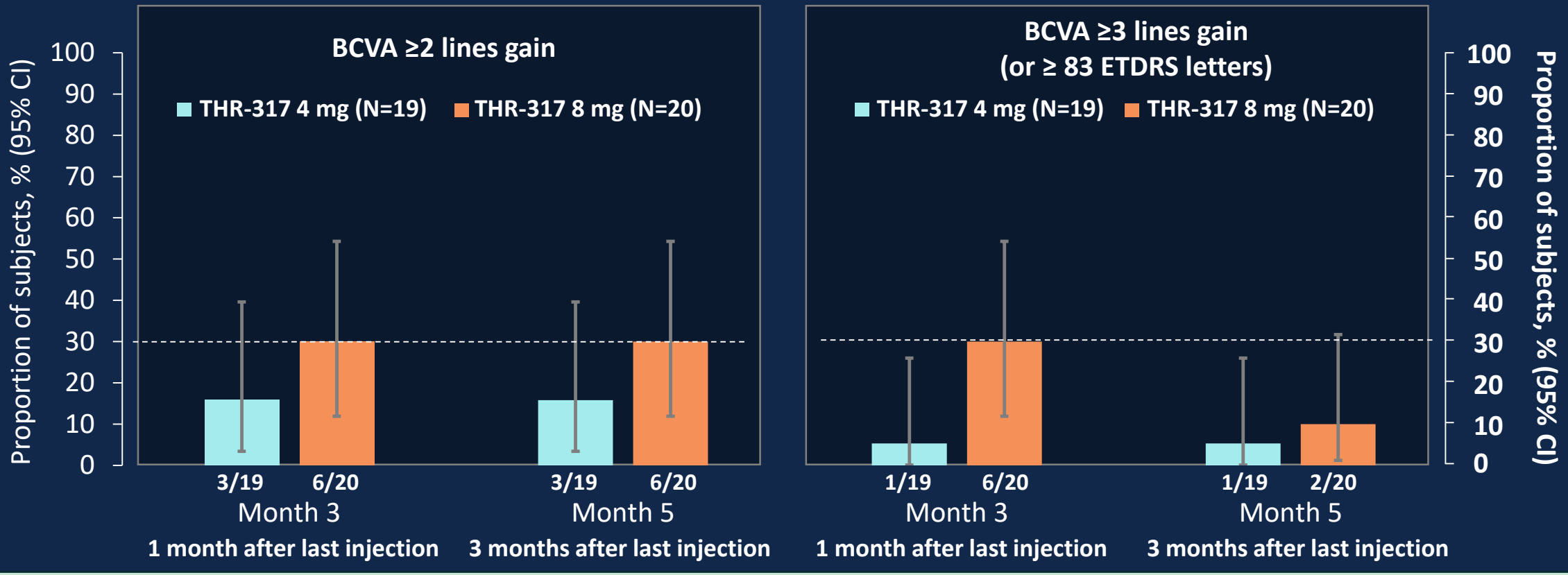
BL, Baseline; PI, post-injection visit (7 days after each injection)

THR-317-001: BCVA Line Gain at Month 3 and Month 5

Anti-VEGF Treatment Naïve Subjects



- More subjects with ≥2 line and ≥3 line gains in the 8 mg arm, at both M3 and M5
- In the 8 mg arm, 30% subjects had a ≥2 line gain at M5, 10% subjects had a ≥3 line gain (≥83 ETDRS letters) at M5
- Majority of subjects with gain at M3 maintained gain to M5

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THR-317-001: BCVA Line Gain at Month 3 and Month 5

Anti-VEGF Treatment Poor Responders

≥2 Line Gainers

- 4 mg arm: 0/4 (0%) at Month 3 and at Month 5
- 8 mg arm: 1/5 (20%) at Month 3 and 1/5 (20%) at Month 5

≥3 Line Gainers

- 4 mg arm: 0/4 (0%) at Month 3 and at Month 5
- 8 mg arm: 1/5 (20%) at Month 3 and 0/5 (0%) at Month 5

- **Small sample size makes conclusions difficult**
- **1 subject had ≥3 lines BCVA gain at month 3, maintained to ≥2 lines at month 5**

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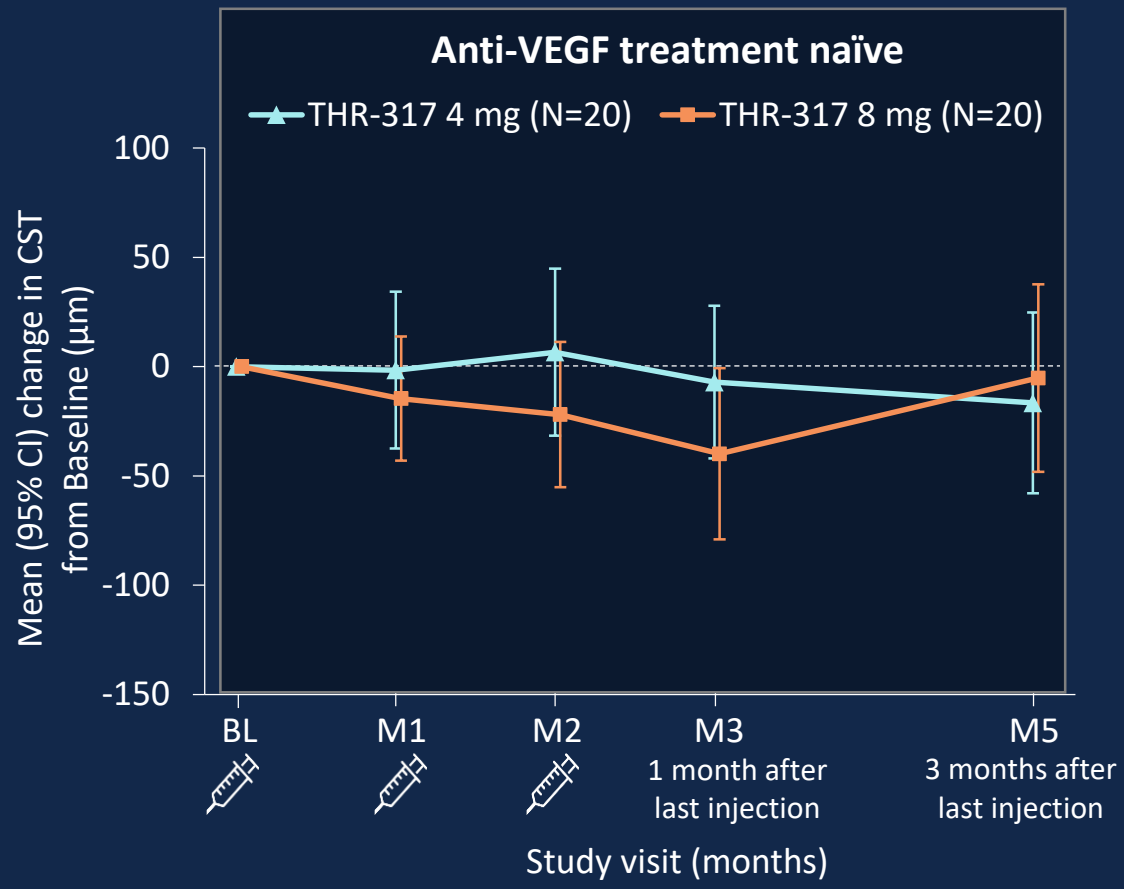
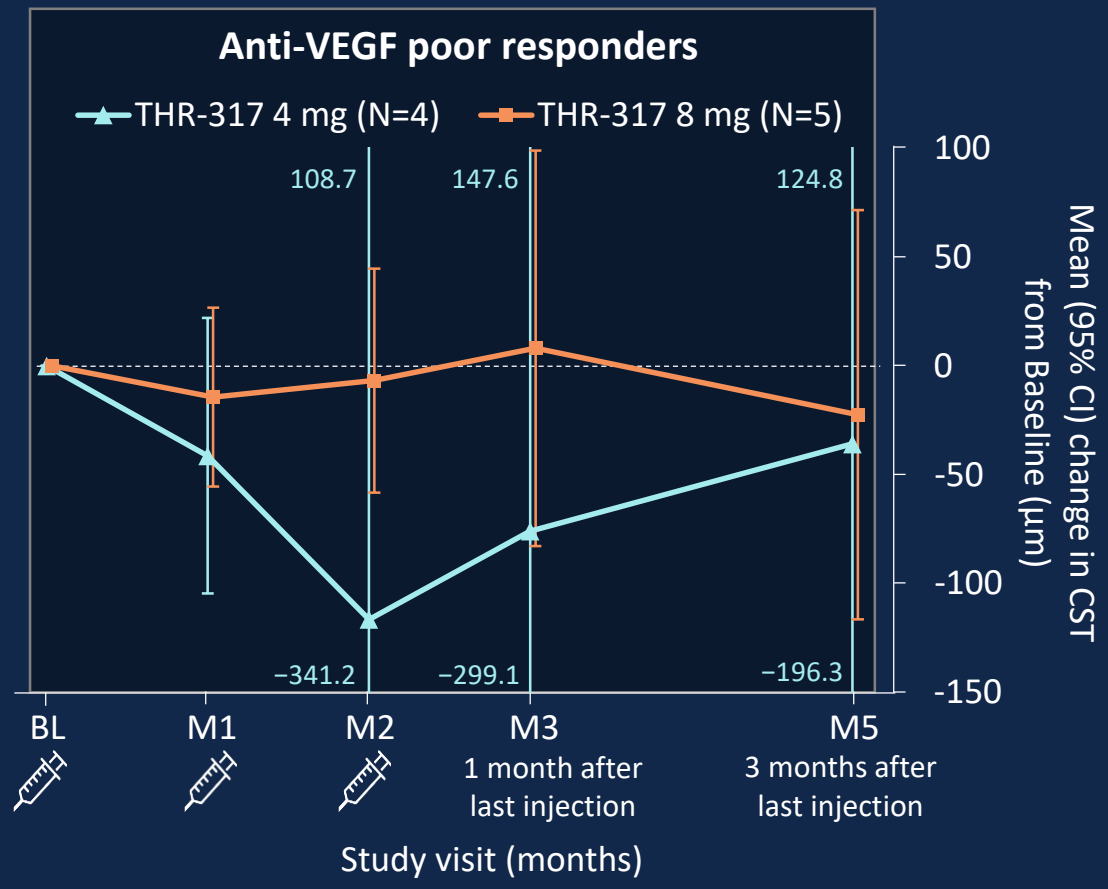
THR-317-001: Mean Change in CST From Baseline





- **Anti-VEGF treatment naïve subjects: Tendency for larger decreases in the 8 mg arm**
- **Anti-VEGF poor responder subjects: Tendency for larger decreases in the 4 mg arm**

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THR-317-001 Conclusions

- 3 monthly intravitreal injections of THR-317 4 mg and THR-317 8 mg were generally safe and well tolerated
- Limited number of AEs, all acute AEs in the study eye were mild in severity and resolved within 1 to 31 days of onset
- Visual gains in both the THR-317 4 mg and 8 mg arms, trend for higher BCVA increases in the THR-317 8 mg arm
- 8 mg dose was selected for future studies
- Study 317-002 (Phase 2 study of 317 in combination with anti-VEGF) is ongoing, results expected H2 2019

Thank you 317-001 Patients and Investigators

- **In total, 49 subjects were treated at 12 sites in Czech Republic, Slovakia and Hungary**

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