A Phase 1 Study of THR-687, an RGD Integrin Antagonist, for the Treatment of Diabetic Macular Edema (DME) in Patients Previously Responsive to anti-VEGF Agents or Corticosteroids*

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*A prospective, Phase 1 (NCT03666923), dose escalation study to evaluate the safety of a single intravitreal (IVT) injection of THR-687 in previously treated subjects with center-involved DME (CI-DME)

MIDWEST EYE INSTITUTE
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Disclosures

Raj K Maturi, MD:

CONSULTING: Neurotech, Oxurion, Aiviva, ForwardVue, Allegenesys, Eli Lilly, DORC International BV

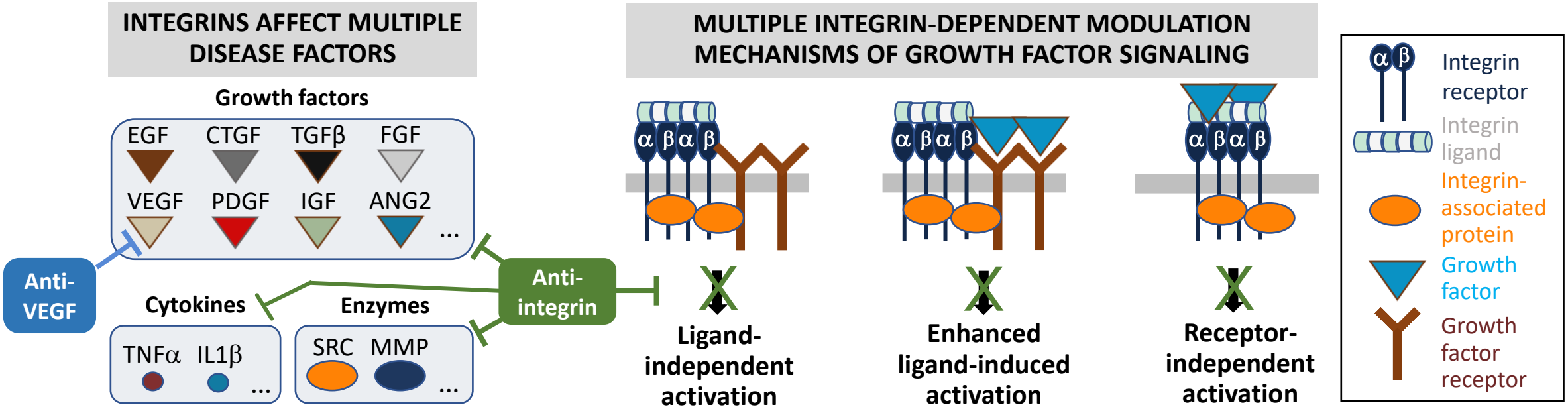
Ownership: ForwardVue

Investigator in clinical trials for:

Allegro Ophthalmics, LLC, Allergan/Abvie, Samsung Bioepis, Oxurion NV, Boehringer Ingelheim Pharma GmbH & Co. KG, Santen Pharmaceutical Co. Ltd., Roche/Genentech, Gyroscope Therapeutics, Glaxosmithkline, Kalvista, Santen, Graybug, , Aerpio

Integrin antagonists have a broad mechanism of action

Integrin antagonists have broader biological effects than anti-VEGF therapies



- Integrins contribute to the activation of multiple growth factor receptors (EGFR, TIE, FGFR, PDGFR, VEGFR, INSR, …)
- Integrin antagonists have the potential to block several pathways simultaneously and therefore to reduce the expression of multiple chemokines, pro-inflammatory cytokines and growth factors

Abbreviations: **ANG2**, angiopoietin-2; **CTGF**, connective tissue growth factor; **EGF**(R), epidermal growth factor (receptor); **FGF**(R), fibroblast growth factor (receptor); **IGF**, insulin-like growth factor; IL1β, interleukin 1 beta; **INSR**, insulin receptor; **MMP**, matrix metalloproteinase; **PDGF**(R), platelet-derived growth factor (receptor); **TGFβ**, transforming growth factor beta; **TIE**, tyrosine kinase with immunoglobulin-like and EGF-like domains; **VEGF**(R), vascular endothelial growth factor (receptor), **TNFα**, tumor necrosis factor alpha;

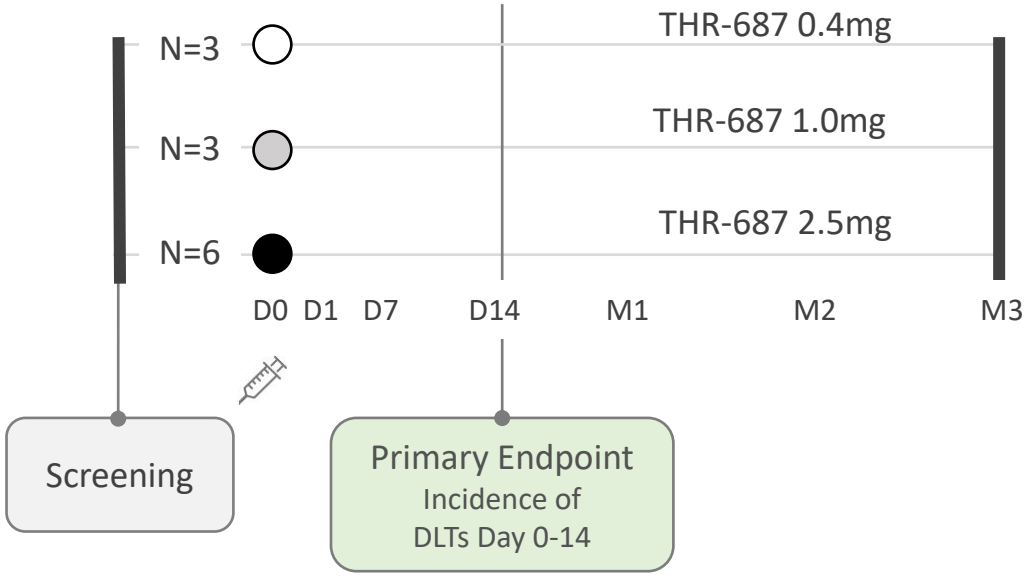
Note: **TIE** is a receptor tyrosine kinase. **Src** is a non-receptor tyrosine kinase and is short for sarcoma.

THR-687-001

Study Design

Total N = 12 subjects with DME

- Center-involved DME; CST ≥ 320 µm (OCT)
- BCVA ≤ 62 and ≥ 23 letters
- History of, and current response to anti-VEGF / corticosteroid treatment



DLT criteria

- Intraocular inflammation: ≥ 2+ inflammation on any of intraocular inflammation grading scales
- BCVA: ≥ 10 ETDRS letter score decrease in BCVA from baseline
- Macular hole

Baseline characteristics in study eye: Mean (SD)	**THR-687 0.4mg N=3**	**THR-687 1.0mg N=3**	**THR-687 2.5mg N=6**	**Overall N=12**
BCVA (ETDRS letters)	59.3 (2.08)	54.7 (2.31)	55.7 (8.26)	56.3 (6.02)
CST (µm)	557.0 (178.41)	612.3 (77.20)	499.0 (154.82)	541.8 (142.08)

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

Abbreviation(s): BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; DLT, dose-limiting toxicity; DME, diabetic macular edema; ETDRS, early treatment diabetic retinopathy study; M, month; OCT, optical coherence tomography

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

All Treated Subjects

Adverse Event	THR-687 0.4mg N=3	THR-687 1.0mg N=3	THR-687 2.5mg N=6	Overall N=12	
	n, [E]	n, [E]	n, [E]	n (%)	E
	1 subject, 2 events	1 subject, 3 events	3 subjects, 4 events	5 subjects, 9 events	
Diabetic Retinal Edema[1]	0	1 [1]	2 [2]	3 (25.0)	3
Conjunctival Hemorrhage[2]	1 [1]	1 [1]	0	2 (16.7)	2
Eye Pain[2]	0	0	1 [1]	1 (8.3)	1
Intraocular Pressure Increased[2]	1 [1]	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

- No deaths, SAEs or DLTs
- No subject had a BCVA loss of ≥ 1 line, at any dose, at any timepoint
- All treatment-related AEs were in the study eye and likely injection-procedure related
- DME worsening was likely due to disease progression

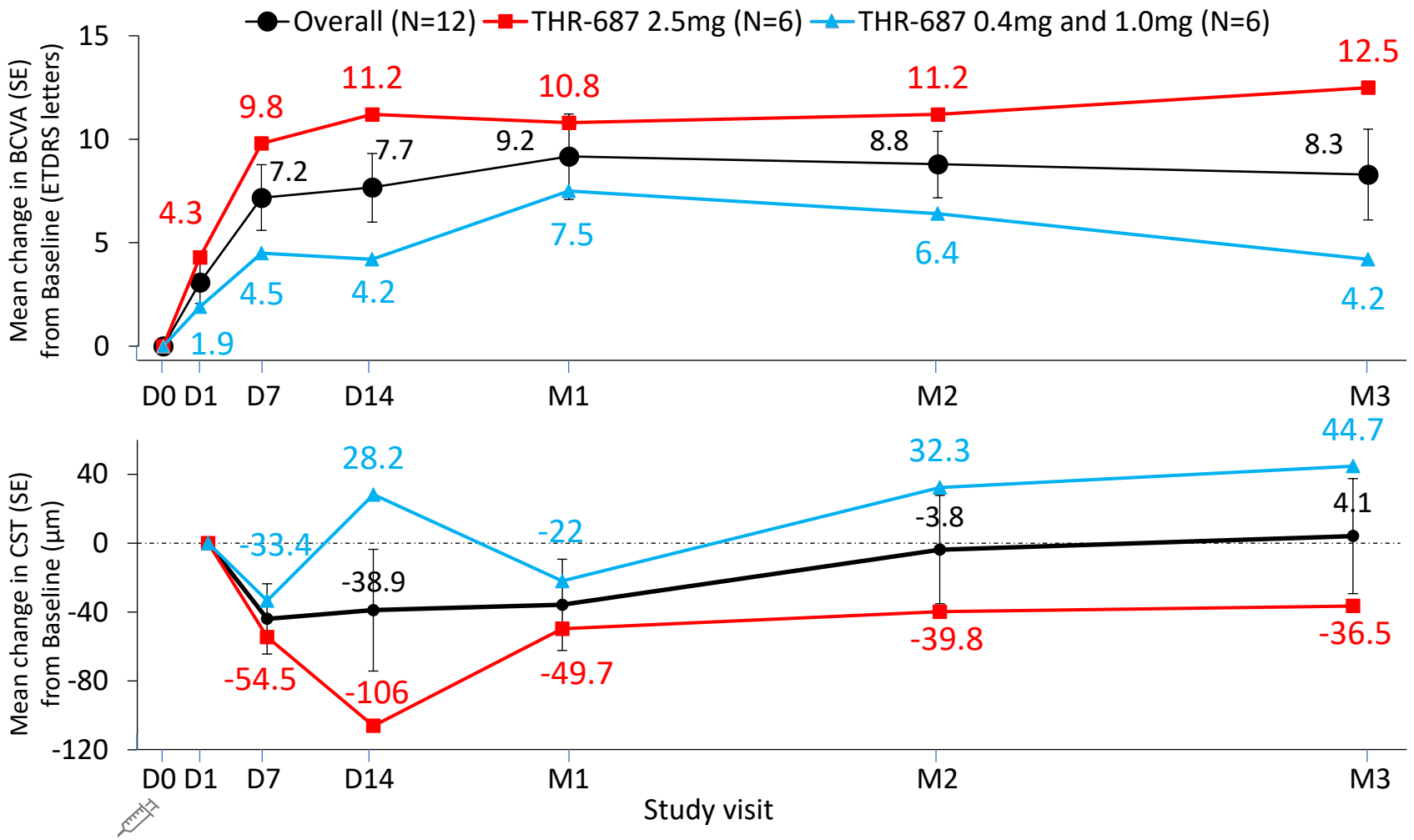
[1]Worsened or persistent DME. Rescue (bevacizumab) administered to one subject in the 1.0 mg group at M2 and two subjects (aflibercept) in the 2.5 mg group (one at M1 and one at M2).

[2] **Deemed treatment-related (drug and/or procedure) by the Investigator**

Abbreviation(s): AE, adverse event; DLT, dose-limiting toxicity; E, number of events; n, number of subjects in category; N, number of subjects; SAE, serious adverse event

THR-687-001: Mean Change from Baseline in BCVA and CST*

All Treated Subjects



BCVA (overall):

- Rapid onset of action as of the day after the injection, with mean 3.1 letters gain
- Highest BCVA gain at Month 1, with mean 9.2 letters gain
- BCVA gain maintained at Month 3, with mean 8.3 letters gain

High dose level had the most pronounced improvement in BCVA, with mean 12.5 letters gain at Month 3

CST (overall):

- Marginal impact on mean CST noted up to Month 1, followed by increases until Month 3

High dose level produced a more pronounced CST decrease of 106 µm at Day 14

* Accounted for rescue: value before rescue carried forward. Rescue was provided for diabetic macular edema and included one subject in the 1.0 mg group who received bevacizumab at M2 and two subjects in the 2.5 mg group who received aflibercept (one at M1 and one at M2).

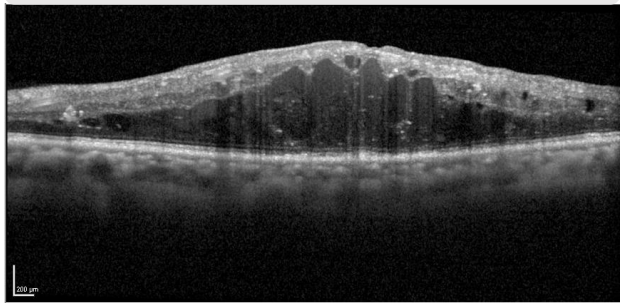
Baseline defined as the day of injection for BCVA and day after injection for CST. SE is only presented for overall data (across dose levels)

Abbreviation(s): BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; ETDRS, early treatment diabetic retinopathy study; M, month; SE, standard error

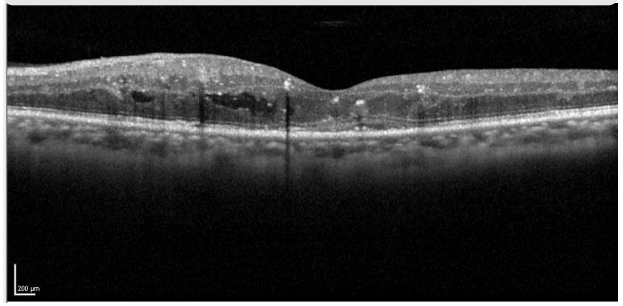
THR-687-001: Individual Subject Data

High Dose Level, CST and BCVA **responder**

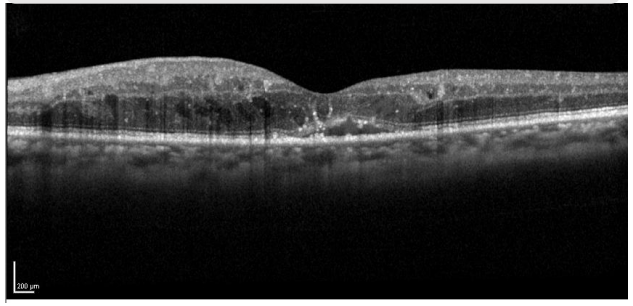
Day 1: CST: 599 µm; **BCVA:** 65 letters



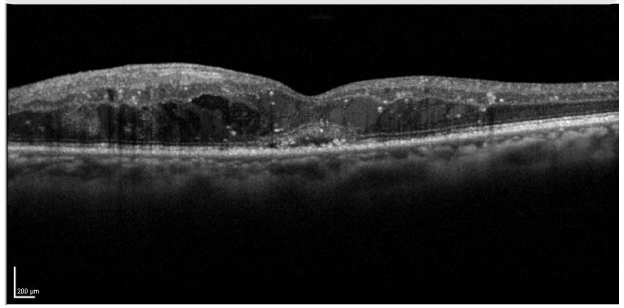
Day 14: CST: 382 µm; **BCVA:** 72 letters



Mo 1: CST: 361 µm; **BCVA:** 74 letters

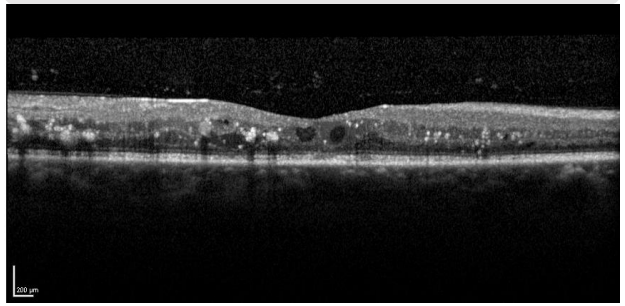


Mo 3: CST: 407 µm; **BCVA:** 72 letters

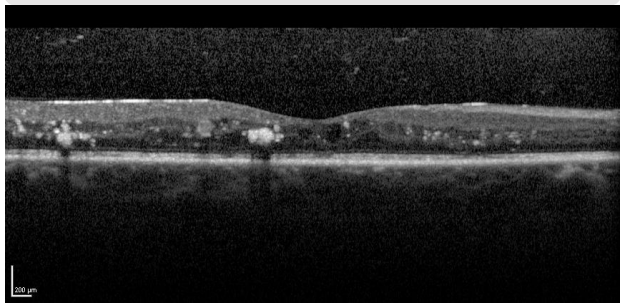


High Dose Level, BCVA responder **without** CST response

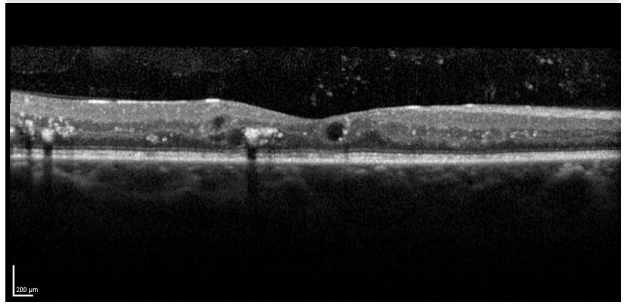
Day 1: CST: 320 µm; **BCVA:** 58 letters



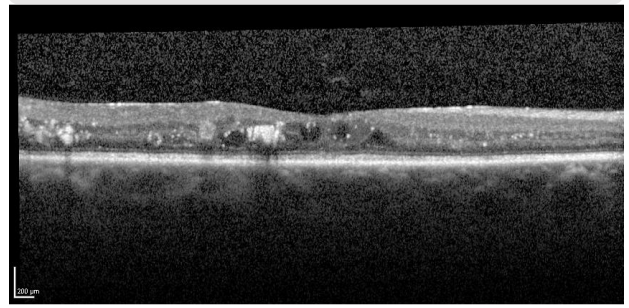
Day 14: CST: 310 µm; **BCVA:** 68 letters



Mo 1: CST: 316 µm; **BCVA:** 75 letters



Mo 3: CST: 304 µm; **BCVA:** 76 letters



Abbreviation(s): BCVA, best-corrected visual acuity; CST, central subfield thickness; Mo, month

THR-687-001: Promising preliminary efficacy results

- **Safe and well tolerated**, without DLTs or serious ocular AEs
- **High dose level had the most pronounced BCVA improvement**, with **mean 12.5 letters gain at Month 3,** as well as more a pronounced **CST decrease of 106 µm at Day 14**
- **Overall, the highest BCVA gain was at Month 1**, with mean **9.2 letters gain**
- **Rapid onset of action as of Day 1**, with mean **3.1 letters gain**
- **BCVA gain maintained at Month 3**, with mean **8.3 letters gain**
- Marginal impact on mean CST noted up to Month 1, followed by increases until Month 3

A multiple dose, multicenter, 2-part Phase 2 study is ongoing to select the dose level of THR-687 and to compare that dose to aflibercept, in treatment-naïve subjects with DME

Abbreviation(s): AE, adverse event; BCVA, best-corrected visual acuity; CST, central subfield thickness; DLT, dose-limiting toxicity