First-in-human Study of THB335, an Oral Small Molecule Inhibitor of Wild Type KIT Receptor Tyrosine Kinase: Initial Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) Results from Single Ascending and Multiple Ascending Dose Cohorts

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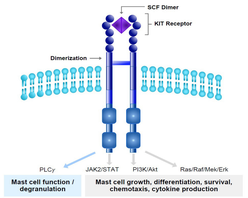
INTRODUCTION

- Mast cells play a central role in allergic diseases and are increasingly linked to other immune-mediated conditions. The short-term activation, long-term proliferation, and survival of mast cells depend upon KIT (CD117) signaling. The inhibition of KIT signaling holds therapeutic potential for mast-cell driven diseases,[1] including chronic spontaneous urticaria (CSU).
- THB335[2] is a novel, orally available, potent, and highly selective wild-type KIT inhibitor that
  - Binds to the tyrosine kinase domain of KIT, blocking downstream signaling by preventing autophosphorylation and subsequent dimerization of the receptor
  - Has low nanomolar KIT potency with excellent kinome selectivity in biochemical and cell-based assays
  - Has peripherally restricted biodistribution
  - Exhibits a favorable nonclinical PK profile, including high oral bioavailability, metabolic stability, and long circulating half-life
- THB335 is being developed to treat mast cell-mediated diseases

THB335 Mechanism of Action



Inhibition of Kinases by THB335

Kinase Target	Biochemical		Cellular
	K_D (nM)	HTRF KIT IC_{50} (nM)	Multiple (nM)
KIT	1.5	16.1	5.0[1] – 7.9[2]
CSF1R	33	56	>3000[3] – >10000[2]
PDGFRα	NT	2710	NT
PDGFRβ	34	737	>3000[4]
ABL1	NT	NT	>10000[2]

[1]M-07e pKIT IC_{50} (KIT); [2]HEK293 nanoBRET EC_{50} (KIT, CSF1R, ABL1, DDR1); [3]M-NFS-60 EC_{50} (CSF1R); [4]A10 EC_{50} (PDGFRβ)

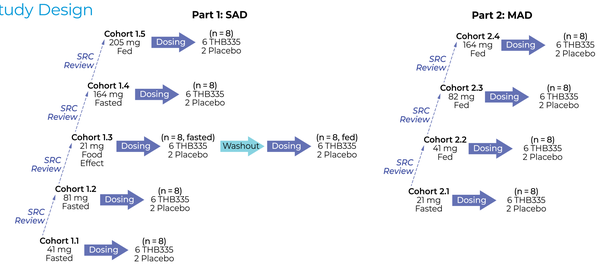
OBJECTIVES

- Assess safety and tolerability
- Characterize pharmacokinetics
- Measure pharmacodynamic effect by serum tryptase and stem cell factor

METHODS

- THB335-101 is a Phase 1, randomized, double-blind, placebo-controlled study
- Part 1: single ascending dose (SAD) and food effects (FE)
  - 5 cohorts with THB335 doses ranging from 21 mg to 205 mg
- Part 2: multiple ascending doses (MAD)
  - 4 cohorts with THB335 doses ranging from 21 mg to 164 mg, administered once daily over 14 days
- Participants were healthy adult males and females, aged 18-65
- Study drug and placebo were administered orally
- Within each cohort in Parts 1 and 2, six participants received active drug (THB335), and two received placebo

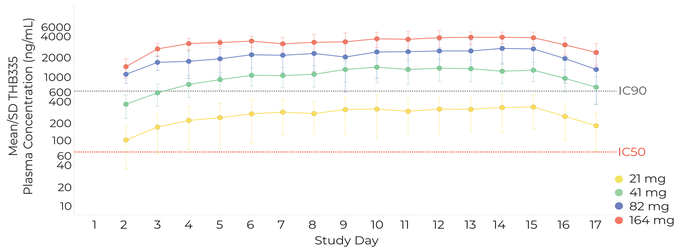
Study Design



Participant Demographics

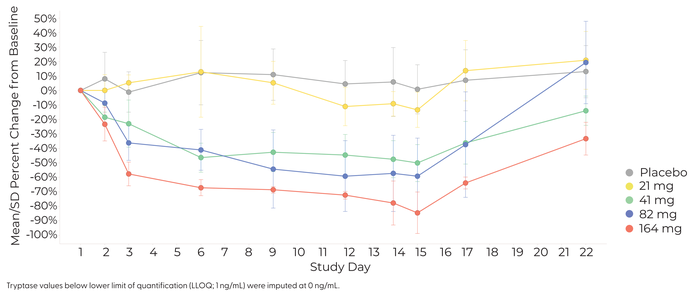
Characteristic		Part 2: MAD				
		Placebo (N = 8)	THB335 21 mg (N = 6)	THB335 41 mg (N = 6)	THB335 82 mg (N = 6)	THB335 164 mg (N = 6)
Age (years)	Median	53.0	55.5	51.5	58.0	56.0
Sex, n (%)	Female Male	8 (100%) 0 (0%)	6 (100%) 0 (0%)	3 (50%) 3 (50%)	6 (100%) 0 (0%)	6 (100%) 0 (0%)
Race, n (%)	White Black /African American	7 (87.5%) 1 (12.5%)	6 (100%) 0 (0%)	5 (83.3%) 1 (16.7%)	6 (100%) 0 (0%)	5 (83.3%) 1 (16.7%)
Ethnicity, n (%)	Hispanic or Latino Not Hispanic or Latino	6 (75%) 2 (25%)	6 (100%) 0 (0%)	2 (33.3%) 4 (66.7%)	6 (100%) 0 (0%)	6 (100%) 0 (0%)
BMI (kg/m²)	Mean	27.7	28.1	28.3	26.3	28.7

RESULTS



MAD Pharmacokinetics

- SAD PK data (not shown) demonstrated dose-dependent increases in drug exposure, with half-life of approximately 40 hours, enabling once daily dosing
- MAD PK data showed dose-proportional increases in exposure that exceed the KIT IC90 at doses of 41 mg daily and higher
- Mild positive food effect
- 41% variability coefficient

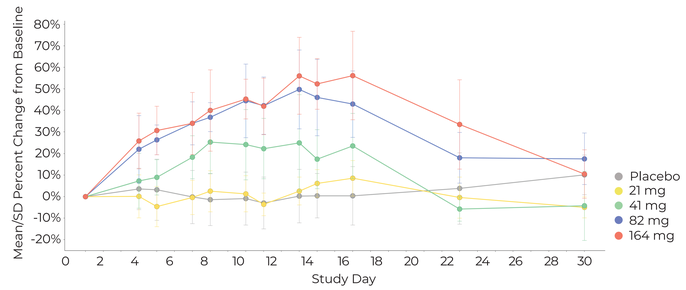


Serum Tryptase

- Dose-dependent decreases in serum tryptase across the MAD cohorts with mean changes from baseline at Day 15 ranging from -13 to -84%
- Peak tryptase reductions occurred at Day 15 across cohorts, indicating maximal PD effect at one day post-dosing completion

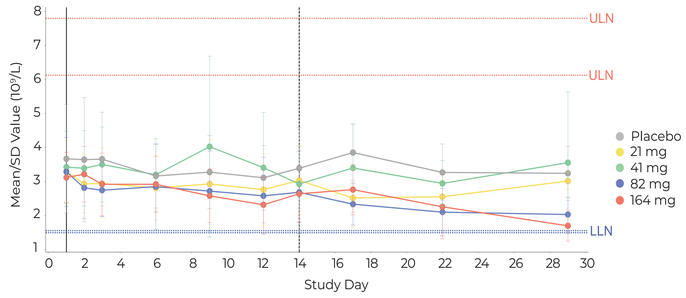
Tryptase values below lower limit of quantification (LLOQ; 1 ng/mL) were imputed at 0 ng/mL.

Figure excludes values for two samples at Day 14 that were apparently switched between participants and 1 sample after discontinuation of 1 subject after day 3 with unrelated hypertension.



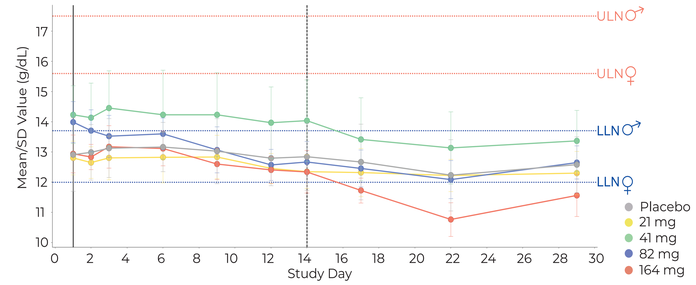
Stem Cell Factor

- Dose dependent increases in SCF observed with similar increases for 82 and 164 mg cohorts



MAD Safety: Neutrophils (ANC)

- Expected on-target dose-dependent reductions in ANC
- All values normalized by follow-up Day 38



MAD Safety: Hemoglobin

- On-target dose-dependent decrease in hemoglobin across the higher-dose MAD cohorts
- Evidence of phlebotomy effect in decreased hemoglobin in placebo participants
- All values normalized by follow-up Day 45

MAD Treatment Emergent Adverse Events in ≥ 2 Participants

Preferred Term of Verbatim	Part 2: MAD					Total
	21 mg THB335	41 mg THB335	82 mg THB335	164 mg THB335	Placebo	
Hemoglobin decreased	0	0	2	5	0	7
Hair color changes	0	0	3	4	0	7
White blood cell count decreased	0	1	1	2	0	4
Neutrophil count decreased	0	1	0	2	0	3
Transaminases increased	0	0	0	1	2	3
Dermatitis contact	1	0	0	0	1	2
Headache	0	1	0	0	1	2

MAD Adverse Events Summary

- Dose-dependent on-target KIT effects observed including mild, reversible, hair color changes in the higher dose cohorts
- Elevated AST and ALT observed in 3 participants: 2 on placebo and 1 active
  - 164 mg cohort AEs (1 in placebo, 1 in active) are largely consistent in time course and similar in magnitude between active and placebo participants and values decline by Day 15, when THB335 exposure remains high
  - Based on data review with DILI experts, transaminitis event in active participant not considered drug-related
- Neutrophil count decreases observed in 1 participant (moderate) in 41 mg cohort and 2 participants (1 moderate, 1 severe) in the 164mg cohort
  - All three participants had baseline neutrophil counts in the lower range of normal limits (below 3 X 10^9/L)
  - White blood cell count changes consistent with changes in neutrophil count
- Hemoglobin decreases observed in 2 participants (both moderate) in 82mg cohort and 5 participants (2 moderate and 3 severe) in the 164 mg cohort
  - Hemoglobin AEs graded using FDA preventative vaccine clinical trial guidance[3] which directs using change from baseline or absolute value at nadir
  - Change from baseline, used by site primary investigator for AE grading, does not take phlebotomy effect into account
  - If absolute values used, then AEs would be Grade 1 or 2 and if NCI CTCAE criteria[4] were used all would be Grade 1

Conclusions

THB335 Phase 1 Clinical Trial Results Summary

- The Phase 1 study achieved its objectives of characterizing the pharmacokinetics, pharmacodynamics, safety, and tolerability of THB335 in a healthy volunteer population.
- Consistent, dose-dependent increases in drug exposure and long half-life support once daily dosing and achieve high levels of target coverage, exceeding the KIT IC90 at daily doses of 41 mg and higher.
- Dose-dependent decreases in serum tryptase (from -13 to -84%) observed along with dose-dependent increases in stem cell factor.
- Safety profile demonstrates expected on-target adverse events consistent with KIT inhibition and may limit use of high dose (164mg) in future clinical studies.
- Moderate, sustained KIT inhibition may allow for evaluation of optimal therapeutic index to evaluate dose levels to determine if there is a range that allows for robust clinical efficacy in mast cell-mediated diseases while minimizing on-target KIT safety effects.
- THB335 has the potential to drive meaningful clinical benefit in patients living with mast-cell mediated diseases including CSU for which Phase 2 planning is underway.

References: [1]. A. Gilreath, L. Tchertanov, M. W. Deininger. Novel approaches to treating advanced systemic mastocytosis. Clin Pharmacol 2019;11:77-92. [2]G. C. Parry, A. Ray, et al. Efficacy of THB001, a Potent and Selective Oral Small Molecule Inhibitor of Wild Type KIT Receptor Tyrosine Kinase, in a Rat Passive Cutaneous Anaphylaxis Model. Poster Presentation (#155); February 2023, AAAAI, San Antonio, TX. [3]U.S. Food and Drug Administration. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: Guidance for Industry (Docket No. FDA-2005-D-0272). Silver Spring, MD: U.S. Department of Health and Human Services; 2007. https://www.fda.gov/media/73679/download. Accessed February 23, 2025. [4]National Cancer Institute, Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Quick Reference [PDF]. Bethesda, MD: National Cancer Institute; 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed February 23, 2025.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; BMI = body mass index; CSU = chronic spontaneous urticaria; DILI = drug induced liver injury; EC_{50} = half maximal effective concentration; FE = food effect; HTRF = homogeneous time resolved fluorescence; IC50 = half maximal inhibitory concentration; IC90 = 90% inhibition concentration; KD = dissociation constant; LLN = lower limit of normal; MAD = multiple ascending doses; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NT = not tested; PD = pharmacodynamic; PK = pharmacokinetic; SAD = single ascending dose; SCF = stem cell factor; SD = standard deviation; ULN = upper limit of normal.

Acknowledgements: Writing, graphic design, and poster production support were provided by Acumen Medical Communications, funded by Third Harmonic Bio.