First-in-human Safety, Pharmacokinetics and Pharmacodynamics of THB001: An Orally Available, Potent and Highly Selective Small Molecule Inhibitor of Wild Type KIT Receptor Tyrosine Kinase

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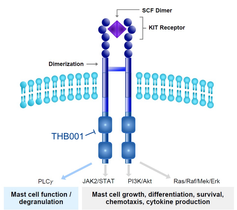
Poster #156

BACKGROUND

Mast cells play a central role in the pathophysiology of allergic diseases. Mast cell activation, proliferation and survival is dependent on KIT (CD117) signaling. THB001 is an inhibitor of wild type KIT being developed as a potential therapy for mast cell driven diseases. A first-in-human study was performed to determine the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of THB001.

THB001 is a highly selective inhibitor of the KIT receptor tyrosine kinase intended for the treatment of mast cell driven diseases[1].

THB001 binds to the tyrosine kinase domain of KIT, preventing autophosphorylation and subsequent dimerization of the receptor, blocking downstream signaling.



Inhibition of Kinases by THB001 in Ba/F3 Assays

Target Kinase	IC_{50} (μM)	Fold Potency vs. KIT
KIT	0.02	-
CSF1R (FMS)	0.95	48
PDGFR-β	2.11	106
PDGFR-α	3.95	198
FLT3	>10.7	>535

Inhibition of KIT results in depletion of mast cells.

Mast cell deactivation is a novel therapeutic approach that should inhibit symptoms of allergic diseases driven by multiple mediators with inadequate response to single agents (e.g. antihistamines, leukotriene antagonists or anti-immunoglobulin E (IgE) antibodies).

METHODS

Study Design

This study was a randomized, placebo-controlled, Phase 1 study in three parts: single ascending doses (SAD, double-blind), food effect (FE, open-label), and multiple ascending doses (MAD, double-blind).

Population

Healthy Volunteers aged 18-65. Vasectomies were required for males enrolled in the MAD only.

Dosing

Oral, gelatin capsule (doses in mg)

- SAD: 10, 30, 100, 300, 600, 400(fed) THB001 (n=32) or PBO (n=10)
- FE: 200 THB001 in fed or fasted state (n=10)
- MAD: 200 QD, 200 BID, 400 BID, 500 QD(fed) THB001 (n=24) or placebo (n=8) for 14 days

Safety Assessments

- Clinical laboratory evaluations: chemistry, hematology, and urinalysis
- 3-lead ECG (telemetry), 12-lead ECG, vital signs
- Physical examination and AE monitoring

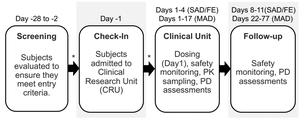
Pharmacokinetics (PK)

- Serial PK sampling on Day 1 (SAD/MAD/FE) and 14 (MAD)
- Pre-dose trough sampling on Days 3-13 (MAD)

Pharmacodynamic Assessments (MAD only)

- Serum Tryptase
- Mast Cell Density

Study Diagram



* Eligible patients who met all the inclusion criteria and none of the exclusion criteria continued with the study

RESULTS

Figure 1. Demographics

Variable	Single Ascending Dose: Placebo (N=10)	Single Ascending Dose: ALL THB001 (N=32)	Food Effect*: 200 mg THB001 (N=10)	Multiple Ascending Dose: Placebo (N=8)	Multiple Ascending Dose: All THB001 (N=24)
Sex, n (%)					
Female	5 (50%)	21 (66%)	6 (60%)	7 (87.5%)	20 (83.3%)
Male	5 (50%)	11 (34%)	4 (40%)	1 (12.5%)	4 (16.7%)
Age (years)					
Median (min, max)	25.0 (18,61)	27.5 (19,62)	36.0 (25,65)	50.0 (27,63)	39.0 (24,64)
Race, n (%)					
Asian	1 (10%)	1 (3%)	1 (10%)	1 (12.5%)	1 (4.2%)
Black/African American	0 (0%)	1 (3%)	1 (10%)	0 (0%)	0 (0%)
White	8 (80%)	30 (94%)	8 (80%)	7 (87.5%)	23 (95.8%)
Other: White/Black	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weight (kg)					
Mean (SD)	76.1 (16.2)	72.3 (11.9)	72.9 (14.3)	64.8 (13.6)	69.8 (10.4)

*Each subject received 200 mg THB001 in a fed and fasted state

Figure 2.Treatment-emergent Adverse Events Reported in >=5% Subjects Overall by MedDRA Preferred Term

Preferred Term n (%)	Single Ascending Dose: Placebo n=10	10 mg THB001 n=6	30 mg THB001 n=6	100 mg THB001 n=5	300 mg THB001 n=4	600 mg THB001 n=5	400 mg fed THB001 n=6	Food Effect: 200 mg THB001 Fed/Fast n=10	Multiple Ascending Dose: Placebo n=8	200 mg THB001 QD n=6	200 mg THB001 BID n=6	400 mg THB001 BID n=6	500 mg THB001 QD Fed n=6
Headache	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (40)	0 (0)	5 (50)	3 (37.5)	2 (33.3)	2 (33.3)	2 (33.3)	4 (66.7)
Hair color changes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33.3)	6 (100)	5 (83.3)	4 (66.7)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	2 (25)	1 (16.7)	2 (33.3)	0 (0)	2 (33.3)
Dizziness	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	2 (40)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (16.7)	0 (0)	4 (66.7)
Fatigue	1 (10)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	2 (20)	2 (25)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)
Myalgia	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	1 (10)	1 (12.5)	0 (0)	0 (0)	1 (16.7)	0 (0)
Rash	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33.3)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (16.7)	0 (0)

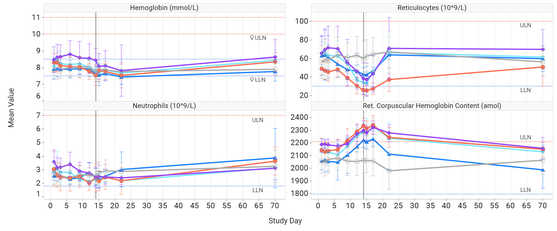
- No severe adverse events or SAEs were reported.
- A total of four moderate AEs were reported: 1 rash reported following discharge in the SAD 400 mg fed cohort; one of cystitis in the MAD 200 mg QD cohort; one of neutrophil count decreased in the MAD 400 mg BID cohort; one of influenza-like illness in the MAD 400 mg BID cohort.
- 1 subject (MAD: 400mg BID) with a low neutrophil count at baseline, discontinued on Day 6 with ANC of 0.9x10^9/L, values recovered by Day 11
- 1 subject (MAD: 500 QD Fed) discontinued on day 12 due to mild anxiety

Note: 5% = 4 or more subjects overall

LEGEND

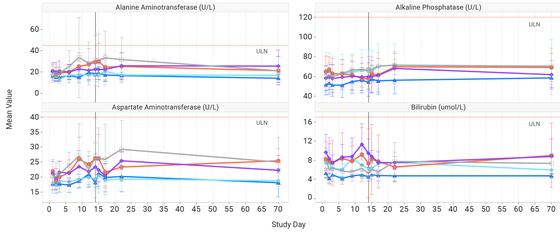
Placebo MAD ▲ 200 mg THB001 QD ★ 200 mg THB001 BID ● 400 mg THB001 BID ◆ 500 mg THB001 QD (Fed)

Figure 3. MAD Hematology Panel Mean/SD



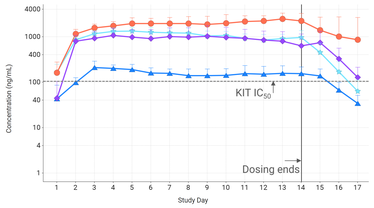
- Mild reductions from baseline in mean neutrophil values were observed at doses above 200 mg QD.
- Reductions observed in reticulocyte counts did not manifest in clinically meaningful reductions in hemoglobin. Compensatory increases in reticulocyte corpuscular hemoglobin content are likely due to mechanisms modulating erythropoiesis (e.g. FLT3 and erythropoietin).

Figure 4. MAD Liver Panel Mean/SD



- There were no adverse transaminase, alkaline phosphatase or bilirubin elevations observed in any subject treated with THB001.
- 1 mild AE of alanine aminotransferase increased was observed in one subject in the in the MAD placebo cohort.
- No differences between treatment groups observed.

Figure 5. MAD THB001 Plasma Trough Concentrations Mean/SD



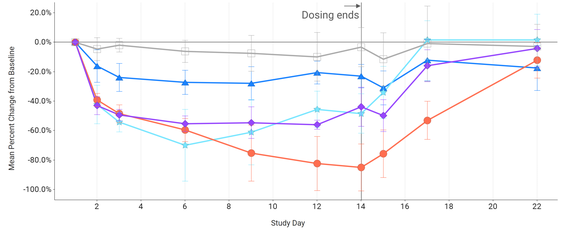
Plasma PK Parameters: Day 14 MAD

PK Parameters[a]	AUC_{0-12} h*ng/mL	C_{trough} ng/mL	t_{max}[b] h	$t_{1/2}$ h
200 mg QD N=6	3120 (34.2)	125 (55.2)	1.25 (1.00, 3.00)	22.4 (30.9)
200 mg BID N=6	9580 (48.0)	538 (54.6)	1.75 (0.50, 2.12)	16.2 (24.5)
400 mg BID N=5	23000 (42.4)	1330 (67.8)	2.00 (1.02, 6.00)	11.5 (24.3)
500 mg QD (Fed) N=5	12000 (82.5)	498 (178.8)	4.02 (3.02, 6.02)	20.4 (26.8)

- THB001 exposure increases were approximately dose proportional (SAD data not displayed), and a long half-life (~20 hours) was observed.
- Mean plasma THB001 exposure increased by approximately 2-fold between the 200 mg and the 400 mg BID cohorts.
- 500 mg QD dosed with food produced a similar steady state profile as 200 BID dosed in a fasted state enabling once daily dosing.
- Steady state trough THB001 concentrations achieved by Day 4 in all cohorts and were ~2 to 20-fold over the KIT IC_{50}

Note: Protein binding adjusted KIT IC_{50}. [a]Geometric Mean (Geometric CV%) [b]Median (Min, Max)

Figure 6. MAD Serum Tryptase Mean Percent Change from Baseline/SD



- Repeat doses of THB001 resulted in dose-dependent decreases in serum tryptase with individual subjects in the 200 mg and 400 mg BID cohorts decreasing to the lower limit of quantitation.
- Reductions were observed by Day 2 with levels restored to baseline for all dose groups by Day 22.

Note: Mean Percent Change from Baseline calculated using "0" for values <LLOQ (1.0)

CONCLUSIONS

- THB001 was safe and well tolerated following a single dose of up to 600 mg and multiple doses of up to 400 mg BID for 14 days with an AE profile consistent with known on-target effects of KIT inhibition such as hair color changes and hematology parameters.
- Mild, asymptomatic reductions in mean neutrophil values from baseline were observed.
- All hair color changes observed in the MAD portion of the study were reversible.
- No clinically relevant changes from baseline were observed in clinical chemistry, urinalyses, vital signs or cardiac parameters as measured by ECG, Holter monitoring, and telemetry.
- Geometric mean peak and overall plasma THB001 exposure (AUCs and C_{max}) increased with increasing THB001 dose levels under fasting conditions; Plasma THB001 exposure increased by ~2.5-fold when given with a meal; QD dosing enabled.
- Treatment with THB001 resulted in significant decreases in serum tryptase which were detectable as early as Day 2 and persisted throughout the dosing period with individual subjects reaching the LLOQ in both the 200 and 400 mg BID cohorts

DISCLOSURES AND AFFILIATIONS

Steven P. Sweeney, Gregg Keaney, Amy DiRico, Edward Conner: Salary: Third Harmonic Bio.; Stock and Options: Third Harmonic Bio.

Stephen Yoo and Graham Parry: Stock: Third Harmonic Bio.

Christine Voors-Pette, Jerome Oude Nijhuis: Funded Research: Third Harmonic Bio; Salary: QPS

Darrell Nix, Nathalie Rioux: Funded Research: Third Harmonic Bio; Salary: Certara

REFERENCES

[1] 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

ACKNOWLEDGEMENTS

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