FOCUSED

On advancing the next wave of medicine for inflammatory diseases

Third Harmonic Bio

MAY 2024

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of, and made pursuant to the safe harbor provisions of, the Private Securities Litigation Reform Act of 1995. Any statements made in this presentation that are not statements of historical fact, including statements about our beliefs and expectations, are forward-looking statements and should be evaluated as such. Forward-looking statements include information concerning the anticipated profile, efficacy and target indications of THB335, the expected timing of clinical trials of THB335 and the expected development and timeline for clinical and non-clinical studies of THB335 candidate. These statements often include words such as “anticipate,” “expect,” “suggests,” “plan,” “believe,” “intend,” “estimates,” “targets,” “projects,” “should,” “could,” “would,” “may,” “will,” “forecast” and other similar expressions. These forward-looking statements are contained throughout this presentation. We base these forward-looking statements on our current expectations, plans and assumptions that we have made in light of our experience in the industry, as well as our perceptions of historical trends, current conditions, expected future developments and other factors we believe are appropriate under the circumstances at such time. As you read and consider this presentation, you should understand that these statements are not guarantees of future performance or results. The forward-looking statements are subject to and involve risks, uncertainties and assumptions, and you should not place undue reliance on these forward-looking statements. Although we believe that these forward-looking statements are based on reasonable assumptions at the time they are made, you should be aware that many factors could affect our actual results or results of operations and could cause actual results to differ materially from those expressed in the forward-looking statements. Factors that may materially affect such forward-looking statements include: our limited operating history and that we have not completed any clinical trials beyond Phase 1 and have not had any product candidates approved for commercial sale; our significant net losses incurred since inception and the likelihood of incurring additional losses for the foreseeable future; our need for substantial additional funding; the early stage of development of our programs and the possibility they may fail in development; our future performance is substantially dependent on our ability to identify and develop future product candidates; legal and regulatory risks; and intellectual property-related risks, among others. Additional risks and uncertainties that could affect our financial results and business are more fully described under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the three months ended March 31, 2024, filed with the SEC on May 15, 2024, and our other SEC filings, which are available on the Investor & Media page of our website at https://ir.thirdharmonicbio.com/ and on the SEC’s website at www.sec.gov. These cautionary statements should not be construed by you to be exhaustive and are made only as of the date of this presentation. We undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise, except as required by applicable law.

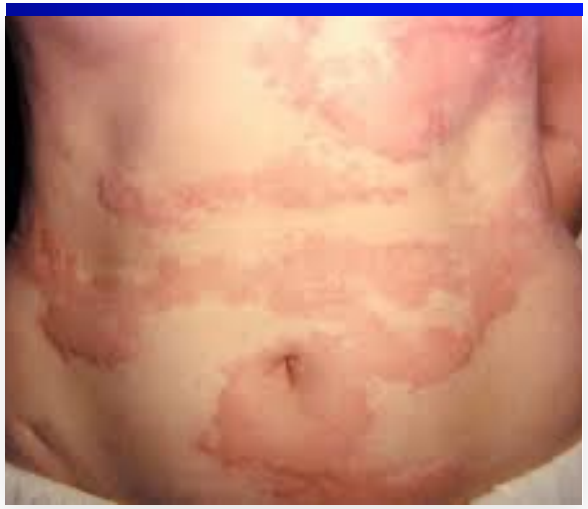
This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Recent Highlights

- THB335 U.S. IND cleared; Phase 1 SAD/MAD trial underway with results expected in 1H’25
- Appointed Chris Dinsmore, Ph.D., to Chief Scientific Officer, Dennis Dean, Ph.D., to Chief Non-Clinical Development Officer and promoted Jennifer Dittman to Chief Development Operations Officer
- Planning rapid advancement to robust Phase 2 study in CSU to support accelerated path to registration studies
- Planned expansion into additional mast-cell mediated inflammatory disorders at Phase 2, including severe asthma
- Next-generation medicinal chemistry efforts continue to support “pipeline-in-a-target” potential
- Cash and cash equivalents of $262.8M as of March 31, 2024

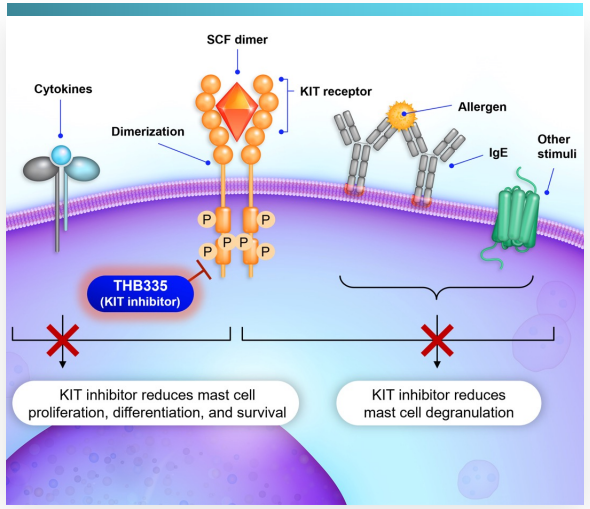
THRD: Focused on KIT to Treat Mast Cell-Mediated Inflammatory Diseases

LARGE ESTABLISHED MARKETS WITH HIGH UNMET NEED



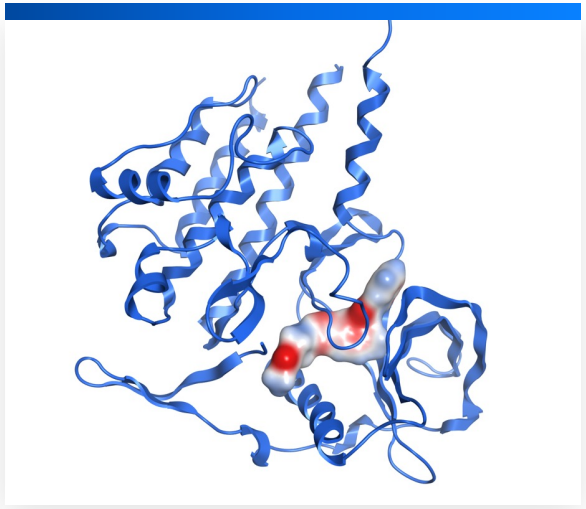
Millions of patients living with severe mast cell-mediated diseases; high residual need despite multiple approved products

KIT: A NOVEL, CLINICALLY VALIDATED TARGET



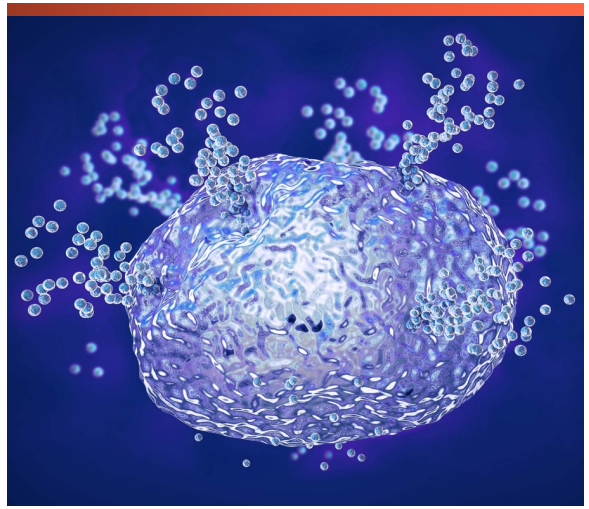
Clinical validation of KIT as potentially transformative target for mast cell-mediated diseases

CLINICAL CANDIDATE: THB335



Highly selective, oral small molecule with potential to optimize therapeutic index and offer patient convenience over injectables

"PIPELINE-IN-A-TARGET" POTENTIAL

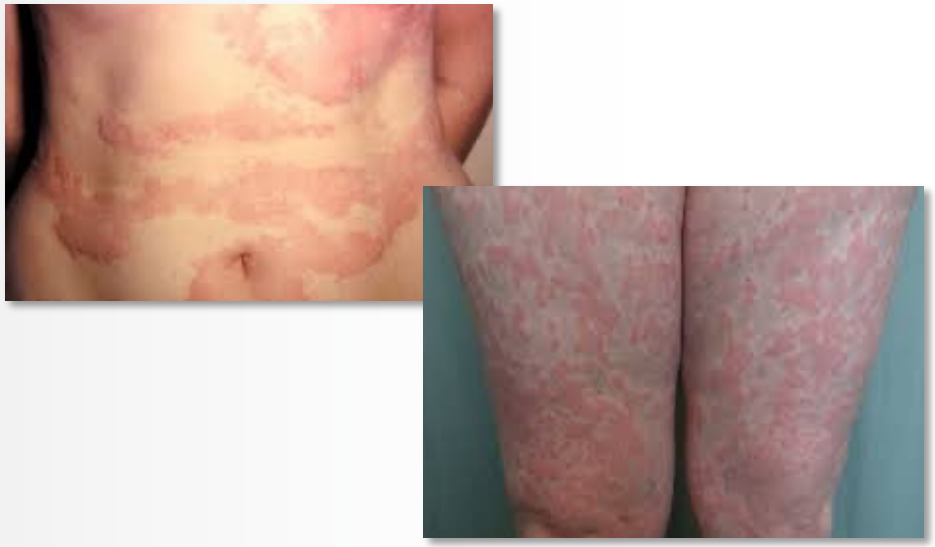


Developing a franchise of KIT inhibitors as potential treatment options for a range of dermal, airway, and GI inflammatory diseases

High Disease Burden in Chronic Spontaneous Urticaria

A severe, yet undertreated dermal inflammatory condition

"Out there, it's a horrible world for urticaria patients"[1]



- **Prevalence:** More than 1.5 million patients or 0.5-1% point prevalence; ~70-80% female, mean age ~46 years
- **Disease impact:** CSU severely impairs quality of life, causes significant physical discomfort and emotional distress, including anxiety, depression, insomnia and social isolation
- **Limited treatment options:** Oral anti-histamines effective in only ~50% of patients; single biologic therapy approved for second-line use
- **New treatment options** are imperative to driving disease awareness, diagnosis and treatment

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[1]Marcus Mauer MD, LifeSci Immunology and Inflammation Day, May 10, 2022

KIT is the Master Regulator of Mast Cell Function and Survival

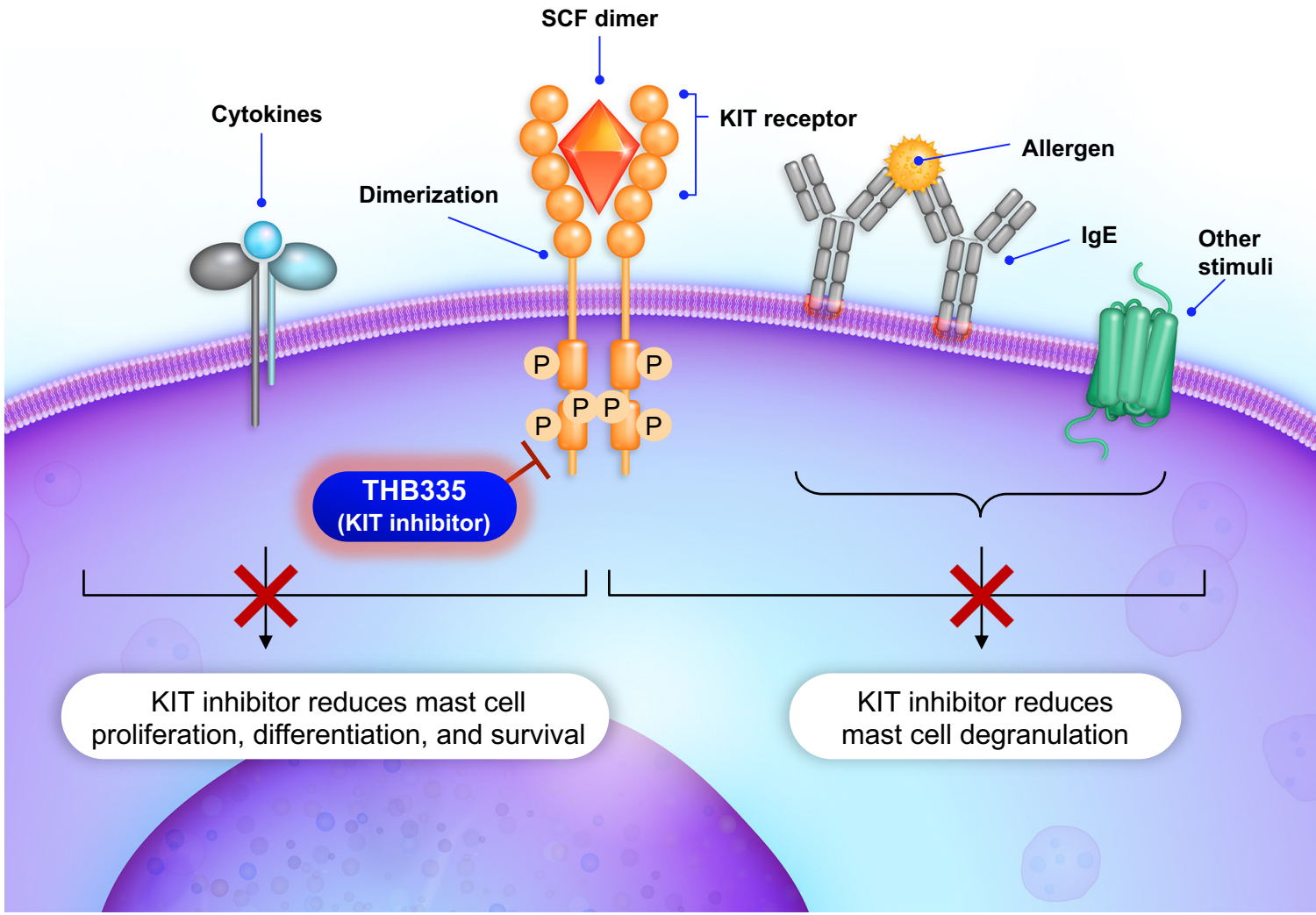
Oral small molecule approach to KIT offers multiple potential therapeutic advantages

KIT

- Targeting mast cell vs specific activating pathways or downstream mediators provides broad approach to addressing disease symptoms
- Emerging clinical validation for potential best-in-disease efficacy in CSU

INTRACELLULAR SMALL MOLECULE INHIBITION

- Potential for therapeutic index optimization
- Patient and medical practice convenience
- Avoids risk of mAb-mediated mast cell activation/anaphylaxis



Early Clinical Proof-Of-Concept Demonstrated With THB001

Discontinued cold inducible urticaria study results

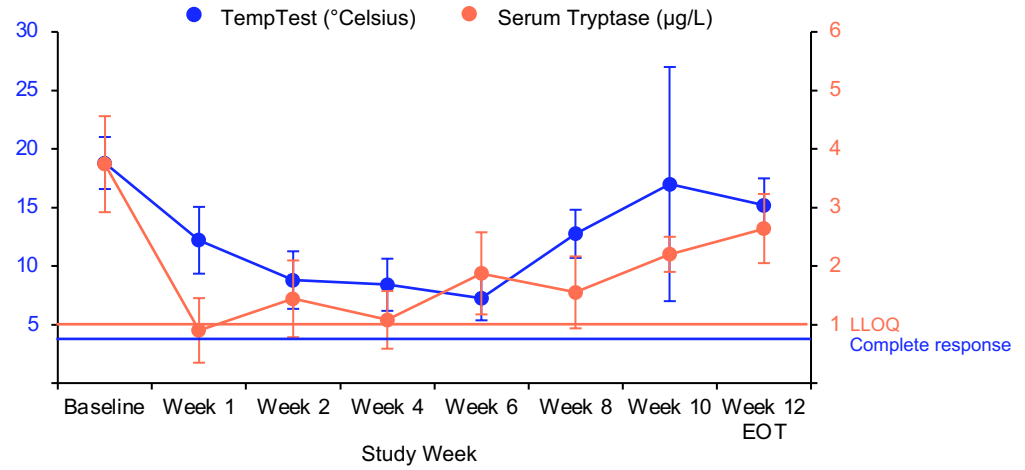
CLINICAL RESPONSES GENERATED AT LOWEST PLANNED DOSE

- Rapid tryptase reduction: -83% mean change from baseline by week 1
- Strong correlation between serum tryptase reduction and clinical response
- 4/5 patients achieved clinical response (2 CRs, 2 PRs) despite early termination of study

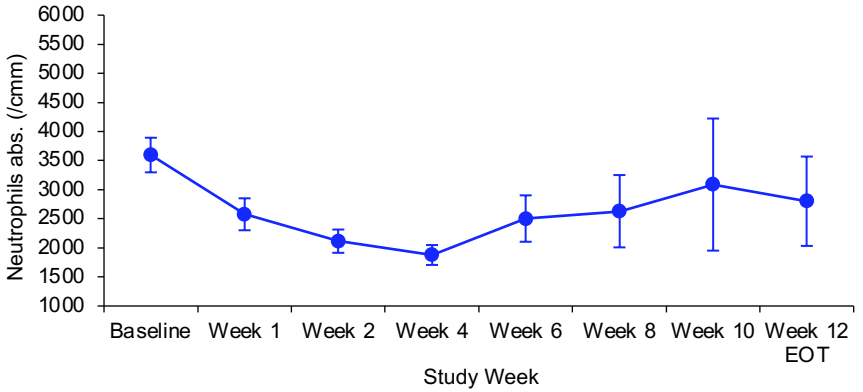
SAFETY SUMMARY

- No serious or severe adverse events (AEs)
- Two moderate AEs of transaminitis which resolved at weeks 17 and 25 of follow-up
- All other AEs were mild, reversible, and consistent with KIT biology

THB001 MEAN TEMPTEST AND SERUM TRYPTASE[1]



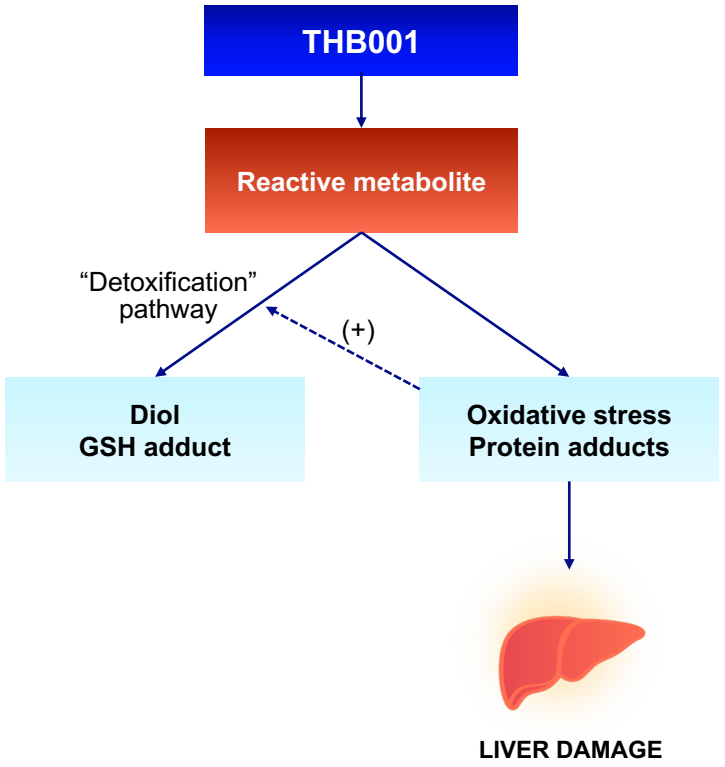
THB001 MEAN ANC BY VISIT[1]



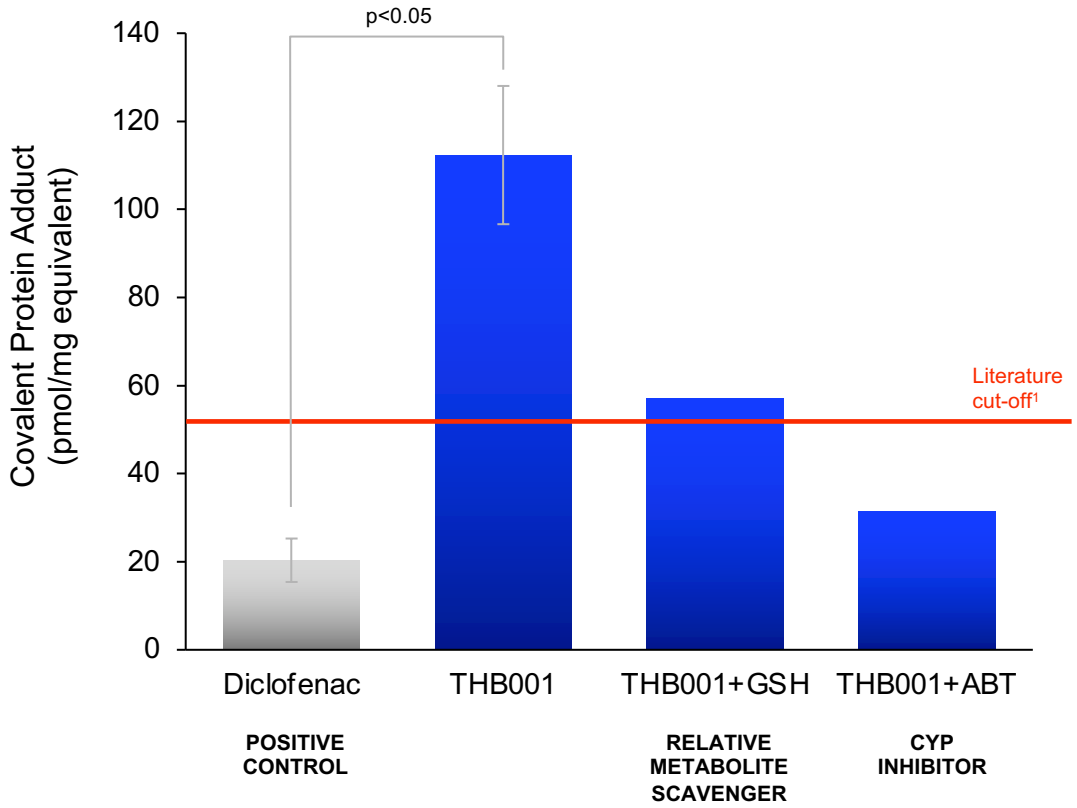
[1] Data are mean +/- SE
ANC = absolute neutrophil count; CR = complete response; EOT = end of treatment; LLOQ = lower limit of quantitation; PR = partial response
Note: Individual subject data available in appendix

THB001 Showed Evidence of Reactive Metabolite Formation

Mechanistic studies provide potential basis for observed transaminitis



[^{14}C] THB001 COVALENT PROTEIN ADDUCT FORMATION IN HUMAN LIVER MICROSOMES IS REDUCED IN THE PRESENCE OF GSH OR CYP INHIBITION



CYP = cytochrome P450; GSH = glutathione

[1] Published literature cut-off: Evans D.C. et al. *Chem Res Toxicol* 2004

THB335: A Next-Generation, Potent, and Highly Selective Wild-Type KIT Inhibitor

U.S. IND cleared with Phase 1 trial underway

THB335 Product Profile

- Low nanomolar KIT potency with excellent kinome selectivity in biochemical and cell-based assays
- Peripherally restricted biodistribution
- Structural and metabolic improvements vs THB001 to address DILI risk
- Favorable nonclinical pharmacokinetic profile, including high oral bioavailability, metabolic stability, and long circulating half-life
- No off-target toxicology findings in IND-enabling studies, consistent with THB001 experience through chronic studies in rodent and non-rodent species
- New composition of matter IP; base patent term through 2043

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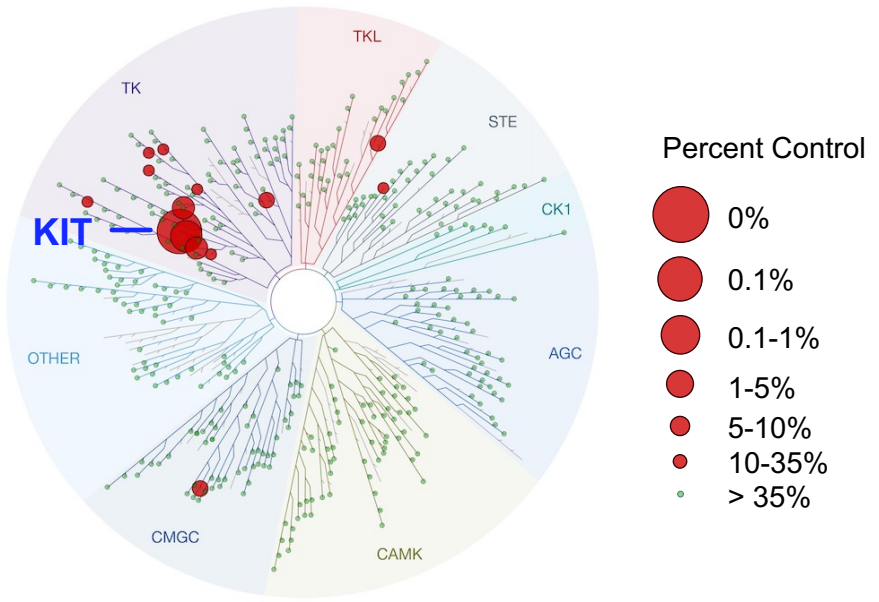
DILI = drug-induced liver injury

THB335 In Vitro Pharmacology Overview

Potent, selective, reversible KIT kinase inhibitor

DiscoverX KinomeSCAN @ 1μM



	BIOCHEMICAL		CELLULAR
Kinase Target	**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]
DDR1	NT	NT	7800[2]
FLT3	>1000	NT	NT

[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)

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THB335 is Metabolically Distinct from THB001

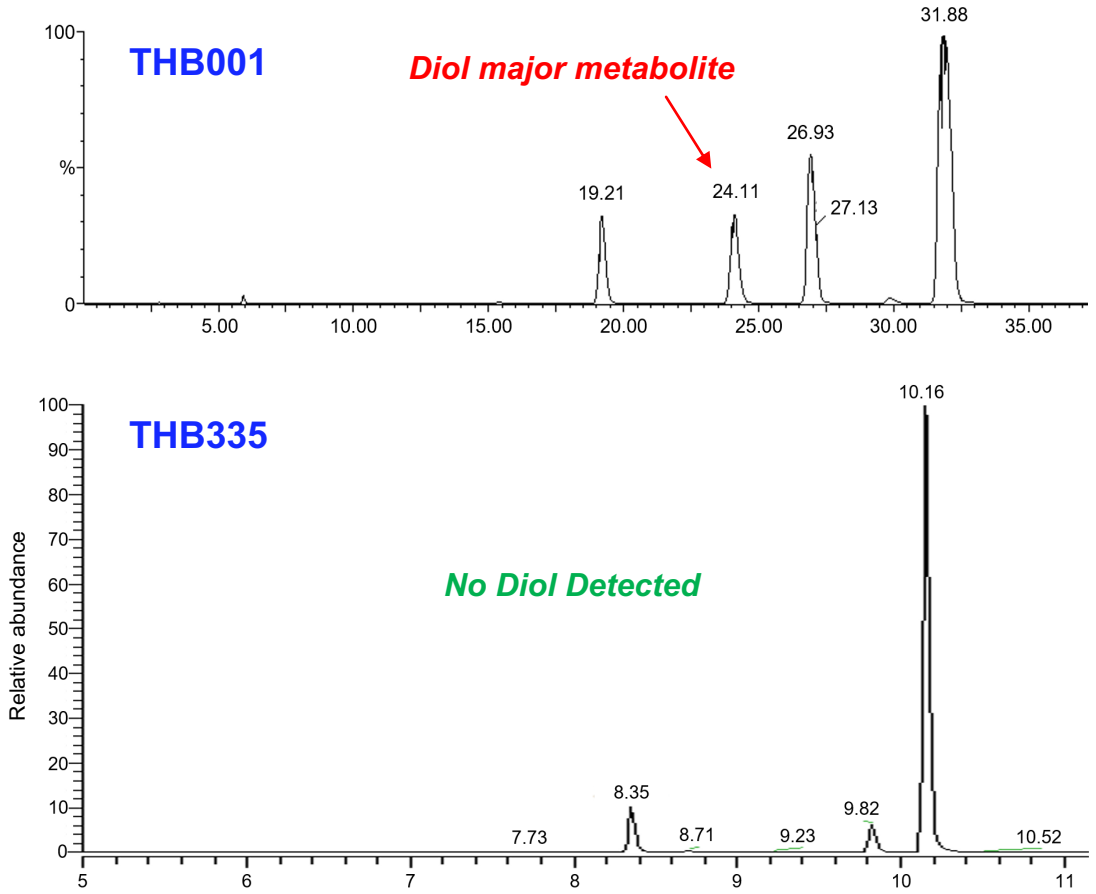
Next-generation structural modifications functionally block the site of reactive metabolite formation

- Diol formed via a reactive epoxide identified as major metabolite of THB001
  - GSH adduct formation associated with detoxification pathways
- Next-generation structural modifications functionally block the reactive metabolic pathway
  - No evidence of diol or GSH adduct formation across species and test systems

			THB001		THB732[1]		THB335	
SYSTEM	SPECIES	ASSAY	GSH	Diol	GSH	Diol	GSH	Diol
In vitro	human	human liver microsomes	+	+	–	–	NT	–
	rat	plasma	+	+	–	–	–	–
In vivo	dog	plasma	+	+	–	–	–	–
	human	plasma	+	+				

MASS SPEC EXTRACTION ION CHROMATOGRAMS

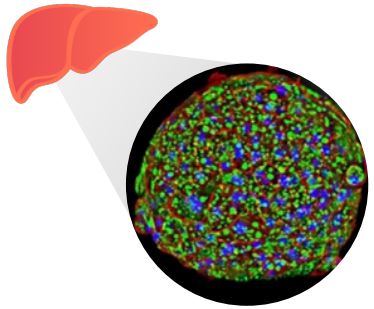
Human Liver Microsomes



[1] THB732 is a next-generation tool compound with high structural similarity to THB335

Next-Gen is Phenotypically Distinct from THB001 in Human Hepatocyte Culture

No evidence for induction of oxidative stress pathways with next-generation analog of THB335

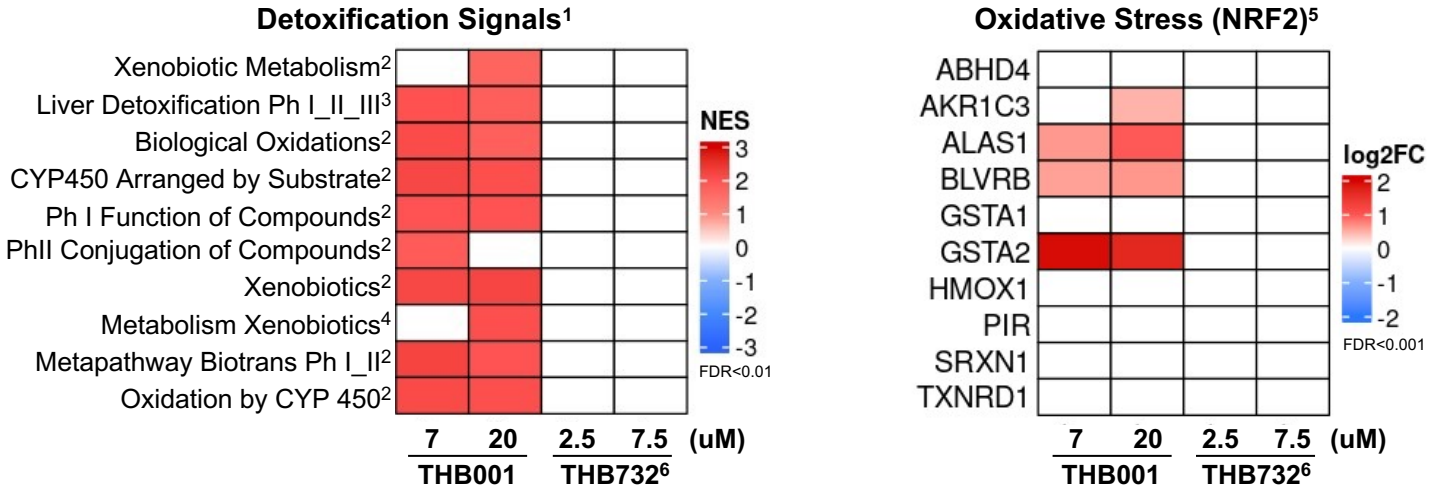


SPHEROID MODEL
Primary human hepatocytes co-cultured with Kupffer and endothelial cells to replicate physiologic liver functions (e.g., drug metabolism, cytokine responses)

21-DAY DRUG TREATMENT
At 100% and 90% cell viability concentrations

TRANSCRIPTOMIC ANALYSIS
Assess changes in gene sets[1,5] associated with detoxification and oxidative stress vs control

BULK RNA SEQ ANALYSIS VS VEHICLE CONTROL AT DAY 21

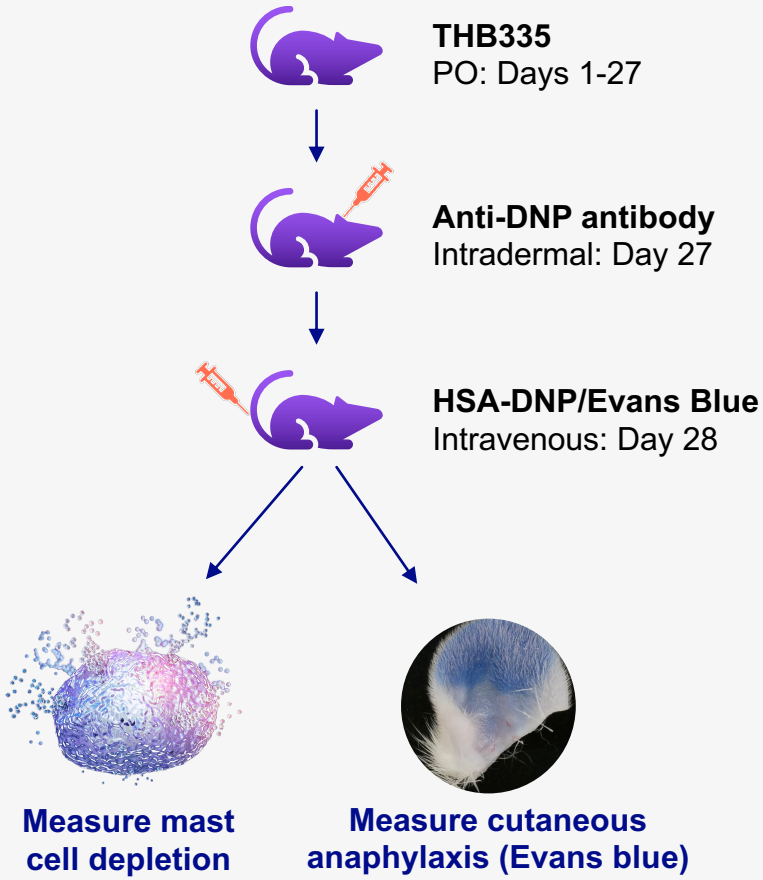


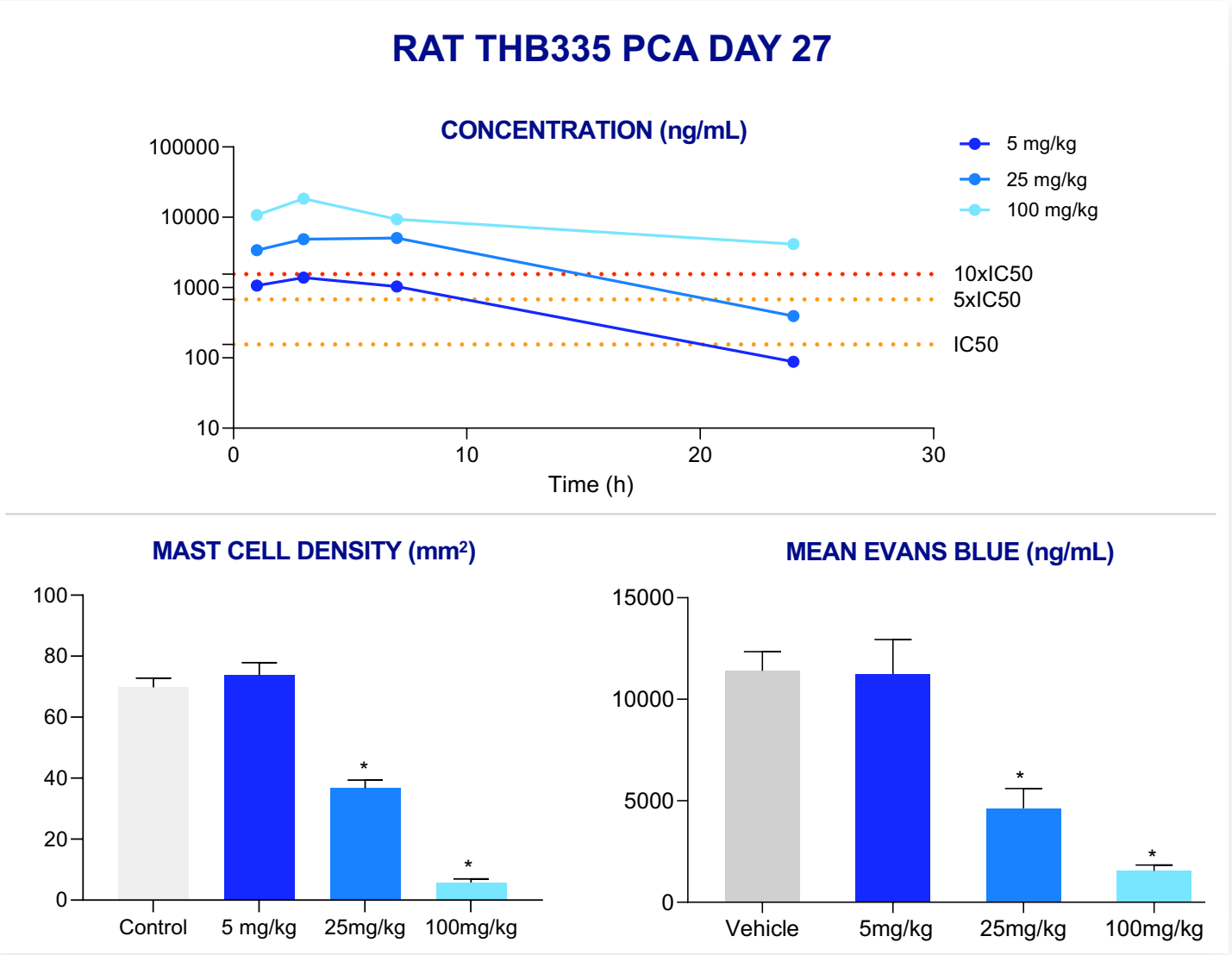
[1]Gene sets derived from [2]Molecular Signatures Database (MSigDB), [3]Insphero and [4]Toxicogenomics.
[5]Kang, W., et al.. Toxicol Sci, 2020. **177**(1): p. 121-139.
[6]THB732 is a next-generation tool compound with high structural similarity to THB335

NES = normalized enrichment score
FDR = false discovery rate
FC = fold change

THB335 Drives Dose-Dependent Mast Cell Depletion and Efficacy In Vivo

Rat passive cutaneous anaphylaxis (PCA) model supports PK/PD correlation across species and test systems





Error bars indicate SEM
* P < 0.0001

Nonclinical Findings of KIT Inhibition Are Well-Characterized Across Programs

Subchronic and chronic toxicology studies of THB001 completed at up to ≥10x clinical exposures

- No evidence of pharmacologically relevant activity against other kinases
- Demonstrated reversibility of all effects

Reproductive toxicology studies completed for THB001

- No functional effect on fertility in either sex at all doses tested

Improved solubility of THB335 enables more rigorous nonclinical toxicology assessments

- IND-enabling studies included doses at >30x predicted exposure margin to clinical doses

Leveraging our experience to prioritize speed to Phase 2 with THB335

- Initiating reproductive and chronic toxicology studies to support rapid advancement toward late-stage clinical development

THB335 Phase 1 SAD/MAD in Healthy Participants

U.S. IND cleared, and trial initiated with data expected in 1H'25

Study Design

- Randomized, placebo-controlled, double-blind, single and 14-day multiple ascending dose design

Key Objectives

- Assess safety and tolerability
- Characterize pharmacokinetics
  - PK modeling based on nonclinical studies completed to-date supports QD dosing
- Measure pharmacodynamic effect characterized by reduction in serum tryptase
  - Highly correlated with clinical response in urticaria studies

Results expected in the first half of 2025

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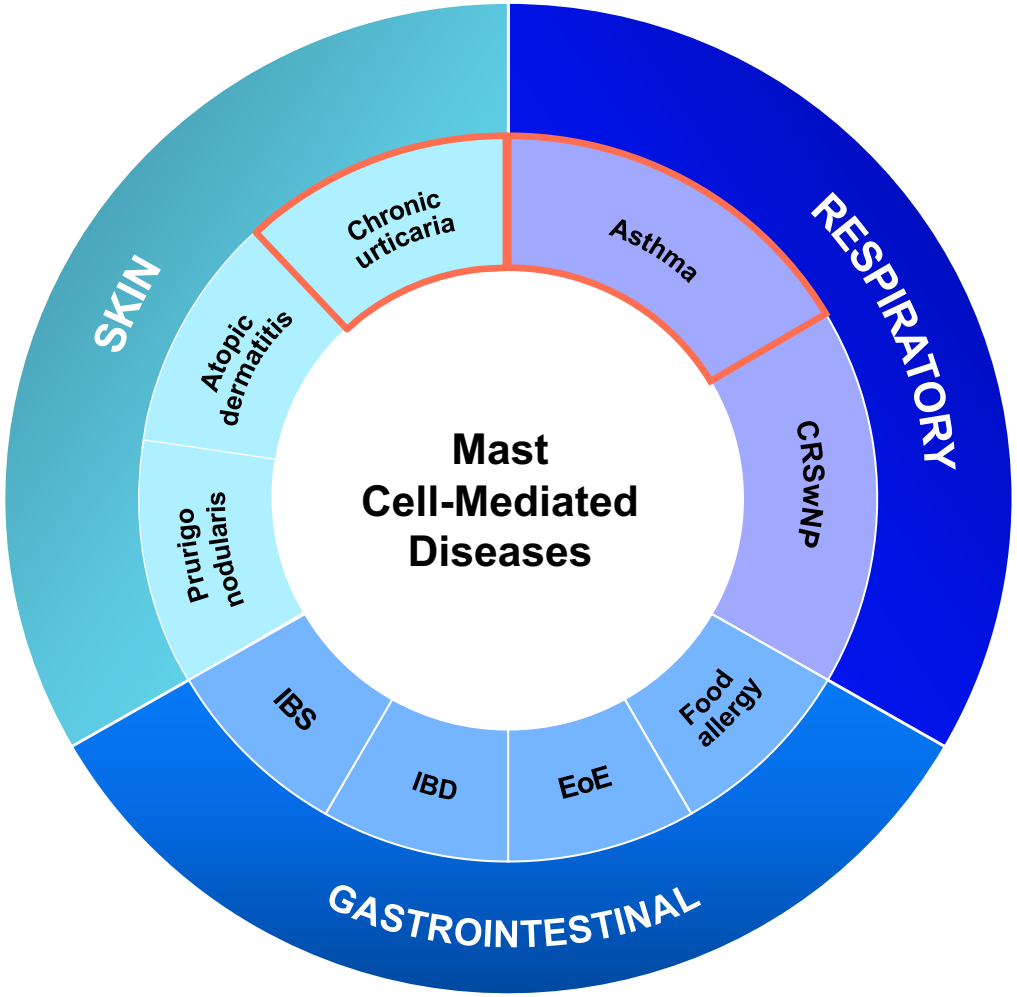
SAD = Single ascending dose; MAD = Multiple ascending dose

“Pipeline-in-a-Target” Potential with KIT Inhibition



- Robust Phase 2 CSU study to support planned direct advancement to Phase 3 registrational studies
- In parallel with CSU, planning to initiate Phase 2 studies in additional mast-cell mediated inflammatory disorders
  - Meaningful opportunity in severe asthma, where mast cells play a central role in pathophysiology and clear need exists for new oral therapies
- Discovery and medicinal chemistry efforts continue to support KIT inhibition franchise expansion
  - Developing differentiated target product profiles to address multiple disease/tissue targets

Third Harmonic Bio Next Steps

Advancing THB335 into the clinic with a longer-term view toward franchise expansion

- THB335 U.S. IND cleared; Phase 1 SAD/MAD trial underway with results expected in 1H’25
- Planning rapid advancement to robust Phase 2 study in CSU to support accelerated path to registration studies
- Planned expansion into additional mast-cell mediated inflammatory disorders at Phase 2, including severe asthma
- Next-generation discovery and medicinal chemistry efforts continue to support “pipeline-in-a-target” potential
- Cash and cash equivalents of $262.8M as of March 31, 2024

APPENDIX

Previously Presented Data

First-Generation THB001 Phase 1b CINDU[1] Study Overview

Discontinued dose escalation study designed to interrogate potential for therapeutic index optimization

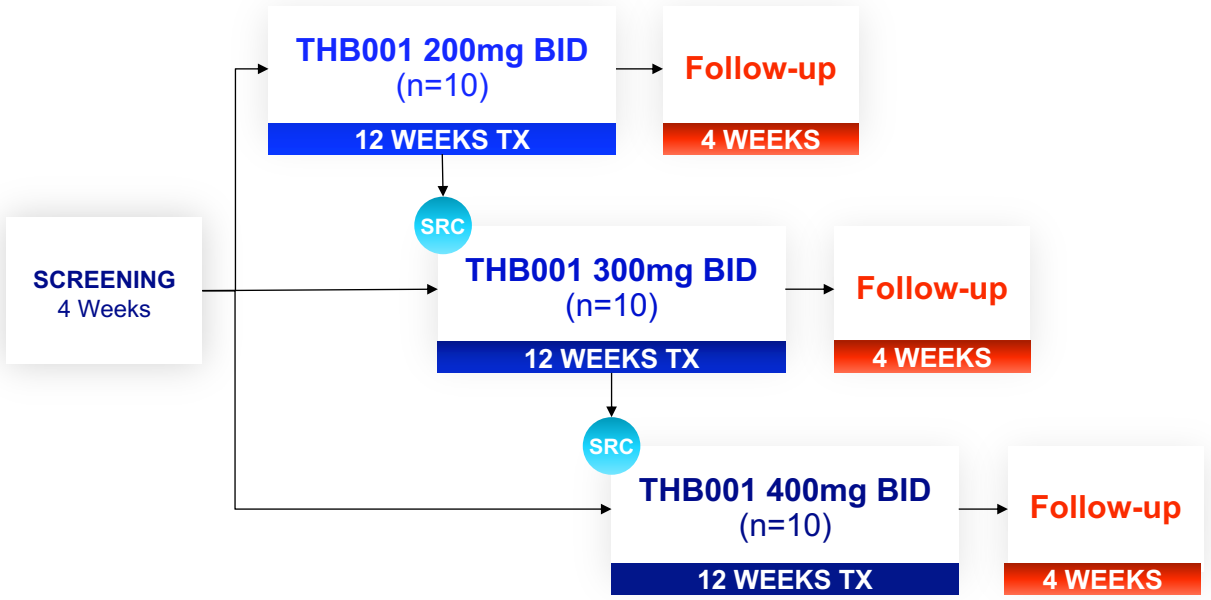
DESIGN AND OBJECTIVES

- 3 doses (1:1:1) of THB001 (total N=30) for 12 weeks
- Pharmacokinetics and serum tryptase levels
- Mean reduction in critical temperature threshold (CTT)

STUDY DISPOSITION

- Enrolled 5 subjects in 200mg BID dose cohort before study discontinuation
- 1 subject completed 12 weeks of treatment
- 2 subjects discontinued at week 8 due to DILI AEs
- 2 remaining subjects were discontinued from study drug at weeks 3 and 4 and were followed for safety

STUDY SCHEMATIC



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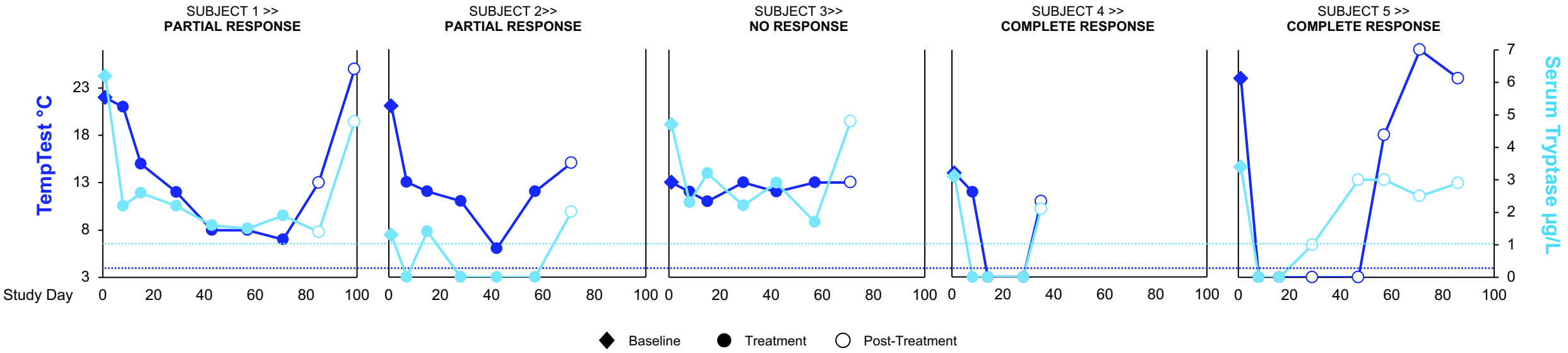
[1]Chronic Inducible Urticaria

SRC=safety review committee

First-Generation THB001 Phase 1b CINDU Study Efficacy Summary

4 of 5 subjects reached partial (n=2) or complete (n=2) responses at lowest planned dose of 200mg BID



- Rapid tryptase reduction: -83% mean change from baseline by week 1
- Strong correlation between serum tryptase reduction and clinical response consistent with other published urticaria clinical data
- 4/5 patients achieved clinical response despite early termination of study

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Note: Negative TempTest results (complete response) are shown at 3° C.
Serum Tryptase values below lower limit of quantitation are shown at 0 µg/L. Empty circles indicate results post treatment.

TempTest complete response ≤ 4°C
Serum lower limit of quantitation = 1 µg/L

First-Generation THB001 Phase 1b CINDU Study Safety Summary

- No serious or severe AEs
- Two moderate AEs of transaminitis which resolved at weeks 17 and 25 of follow-up
- All other AEs were mild
  - Overall profile consistent with on-target effects of KIT inhibition observed in the Phase 1a study (e.g., hair color change)
  - Hematologic profile similar to Phase 1a and trend toward stabilization of values observed as expected

THB001 HEMATOLOGY

Hemoglobin and neutrophil count by subject over time