



## Third Harmonic Bio Announces Next-Generation Oral KIT Inhibitor Product Candidate THB335

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*THB335 retains selectivity and potency of first-generation oral KIT inhibitor, THB001, with differentiated metabolic, distribution and physicochemical profile*

*THB001 demonstrated evidence of pharmacodynamic (PD) activity and clinical benefit in discontinued Phase 1b study in chronic inducible urticaria*

*Extensive nonclinical studies of THB001 identified a potential mechanistic basis for observed hepatotoxicity; structural modifications introduced in THB335 believed to address this risk*

*U.S. Investigational New Drug (IND) Application filing and initiation of clinical trials of THB335 planned for the first half of 2024*

SAN FRANCISCO, July 25, 2023 (GLOBE NEWSWIRE) -- Third Harmonic Bio, Inc. (Nasdaq:THRD), a biopharmaceutical company focused on advancing the next wave of medicine for inflammatory diseases, today announced its next-generation product candidate, THB335, a potent, highly selective oral small molecule KIT inhibitor with a meaningfully differentiated product profile as compared to the company's first-generation product candidate THB001. Third Harmonic plans to file a U.S. IND and initiate clinical development of THB335 for the treatment of mast cell-mediated inflammatory diseases during the first half of 2024.

The company also disclosed topline results of the Phase 1b clinical trial of THB001 for the treatment of chronic inducible urticaria, which was discontinued in December 2022 due to observed liver transaminitis in two of five patients enrolled. The results demonstrated evidence of clinical benefit in four of the five patients, achieving partial or complete responses despite early termination of the trial.

In addition, the company shared preliminary results from extensive studies of THB001 that were conducted to identify the mechanism for the observed liver toxicity, which was not predicted by nonclinical toxicology studies. These in-depth studies identified a metabolic pathway resulting in the formation of an intermediate reactive metabolite. Reactive metabolite formation has been previously implicated as a mechanistic basis for drug-induced liver injury. Structural modifications introduced into THB335 are believed to address this risk and studies conducted to date support its differentiated metabolic profile.

"Based on extensive studies of our first-generation product candidate, THB001, we selected THB335, a next-generation compound that incorporates structural modifications which we believe maintain the potency and selective KIT inhibitory activity of THB001, while improving its safety profile," said Natalie Holles, Chief Executive Officer of Third Harmonic Bio. "In addition, we are very encouraged by the clinical efficacy results observed in the discontinued Phase 1b study of THB001, demonstrating clinical responses in four out of five patients enrolled in the lowest planned dose cohort of the study. The combined structural modification and efficacy data give us confidence that we have the potential in THB335 for the optimal therapeutic profile against KIT for the treatment of mast cell-mediated inflammatory disorders. We are currently executing on our plans to be back in the clinic during the first half of next year."

### **THB001 Clinical Results**

The Phase 1b clinical trial of THB001 in chronic inducible urticaria was designed to evaluate the preliminary safety and tolerability, efficacy and pharmacokinetics of three dose levels of THB001 over 12 weeks of treatment. Five patients were enrolled in the lowest planned dose cohort of 200mg BID before study discontinuation. The first patient enrolled completed 12 weeks of treatment; the next two patients enrolled were discontinued from study drug at week eight due to observed liver transaminitis. The two remaining patients were discontinued from study drug at weeks three and four and followed for safety per the trial protocol.

The transaminitis adverse events (AEs) were reported as moderate and resolved at weeks 17 and 25. All other AEs were reported as mild and demonstrated to be reversible. The overall AE profile, including mild hematologic and hair color changes, was consistent with the known on-target effects of KIT inhibition.

Rapid and sustained reduction in serum tryptase, a serum biomarker associated with mast cell activation and correlated with clinical response in urticaria studies, was observed in the trial, with an 83.1% mean change from baseline by week one. Four out of the five patients treated in the study achieved partial (n=2) or complete (n=2) Critical Temperature Threshold responses despite early termination of dosing.

The company plans to present the full results of the study at a scientific conference later this year.

### **THB335**

THB335, the company's next-generation oral small molecule wild-type KIT inhibitor product candidate, retains the potency and selectivity profile of THB001, with structural modifications which are expected to mitigate the hepatotoxicity risk as well as provide a differentiated metabolic, distribution and physicochemical profile.

Key attributes of THB335:

- Nanomolar potency against KIT
- High degree of selectivity against closest related kinases, including PDGRF and CSF1R, as measured by biochemical assays and confirmed in cell-line viability assays
- No evidence for reactive metabolite formation as observed with THB001

- High oral bioavailability and metabolic stability
- Improved peripheral restriction compared to THB001 (decreased CNS penetrance)
- Improved solubility and lipophilicity compared to THB001
- Favorable pharmacokinetic profile with long circulating half-life

The company plans to file a U.S. IND and initiate clinical trials of THB335 in the first half of 2024. Phase 2 development is expected to initially focus on chronic spontaneous urticaria, with planned expansion into other mast-cell mediated inflammatory disorders.

As previously reported, Third Harmonic Bio had \$282.2 million in cash and cash equivalents as of March 31, 2023.

**About Third Harmonic Bio, Inc.**

Third Harmonic Bio is a biopharmaceutical company focused on advancing the next wave of medicine for inflammatory diseases through the development of novel highly selective, oral small-molecule inhibitors of KIT, a cell surface receptor that serves as the master regulator of mast cell function and survival. Early clinical studies demonstrate that KIT inhibition has the potential to revolutionize the treatment of a broad range of mast-cell-mediated inflammatory diseases, and that a titratable, oral, intracellular small molecule inhibitor may provide the optimal therapeutic profile against this target. Third Harmonic's lead product candidate THB335 is expected to enter clinical trials during the first half of 2024. For more information, please visit the Third Harmonic Bio website: [www.thirdharmonicbio.com](http://www.thirdharmonicbio.com).

**Forward-Looking Statements**

This press release contains "forward-looking" statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the expected product profile of THB335 as compared to THB001, the timing of filing a U.S. IND application for THB335, the expected timing for clinical activities, and the expected timing to present studies and results related to THB001. Forward-looking statements can be identified by words such as: "anticipate," "intend," "plan," "goal," "seek," "believe," "project," "estimate," "expect," "strategy," "future," "likely," "may," "should," "will" and similar references to future periods. These statements are subject to numerous risks and uncertainties, including risks and uncertainties related to Third Harmonic Bio's cash forecasts, ability to advance its product candidates, the receipt and timing of potential regulatory submissions, designations, approvals and commercialization of product candidates, our ability to protect our intellectual property, the timing and results of preclinical and clinical trials, changes to laws or regulations, market conditions, geopolitical events, and further impacts of pandemics or health epidemics, that could cause actual results to differ materially from what Third Harmonic Bio expects. Further information on potential risk factors that could affect Third Harmonic Bio's business and its financial results are detailed under the heading "Risk Factors" included in Third Harmonic Bio's Quarterly Report on Form 10-Q for the three months ended March 31, 2023, filed with the U.S. Securities and Exchange Commission (SEC) on May 11, 2023, and in Third Harmonic Bio's other filings filed from time to time with the SEC. Third Harmonic Bio undertakes no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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