An Open-label, Multicenter Study to Assess the Safety, Pharmacokinetics and Pharmacodynamic Effects of THB001 in Adult Patients with Chronic Cold Urticaria

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• To evaluate the safety and tolerability of THB001 in cold induced chronic urticaria patients

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON51543

Source
ToetsingOnline

Brief title
A study for the safety, PK and PD of THB001 in cold urticaria patients

Condition

- Allergic conditions

Synonym
Cold hives, Cold urticaria

Research involving
Human

Sponsors and support

Primary sponsor: Third Harmonic Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Mast cells, Multi-national, Open-label, Urticaria

Outcome measures

Primary outcome

• Treatment emergent AEs/SAEs

• Laboratory assessments

• ECG, vital signs

Secondary outcome

• Change from baseline in critical temperature threshold (CTT) over time using

the TempTest® system

• Percentage of complete responders (CTT <= 4°C) and partial responders

(> 4°C CTT change from baseline) over time

• Time to complete (partial) response

• Pre- and post-treatment changes in skin mast cell density

• Pre- and post-treatment changes in serum tryptase

• Plasma PK concentration of THB001 over time

• Modeled plasma PK parameters of THB001 including but not limited to Cmax,

Cmin and AUC as appropriate

Study description

Background summary

This planned phase 1b trial will be performed to evaluate the safety, pharmacokinetics, and pharmacodynamics of up to 3 dose levels of THB001 over 12

weeks in the treatment of patients with ColdU. Targeting mast cells with THB001 is expected to provide clinical benefit in ColdU by decreasing the number of mast cells and their activity. Since mast cells are the primary effector cell in CIndU and with early clinical data demonstrating reduction of serum tryptase, THB001 should reduce wheal responses in ColdU measured as change in critical threshold temperature (CCT). Treatment effects will be evaluated through Patient Reported Outcome (PRO) measures and skin biopsies for evaluation of mast cell numbers.

This represents a novel therapeutic approach. Existing therapies generally target individual mast cell mediators, such as histamine, leukotrienes, and/or mast cell activation pathways (IgE) and many patients have inadequate response. THB001 is intended to deplete the mast cells and thereby inhibit multiple mediators of symptoms of ColdU or other allergic diseases.

Study objective

• To evaluate the safety and tolerability of THB001 in cold induced chronic urticaria patients

Study design

This is a phase 1b, open label, non-randomized, sequential dose-escalation, multicenter trial in adult patients with cold induced chronic urticaria.

Intervention

THB001 200 mg BID for 12 weeks
THB001 300 mg BID for 12 weeks
THB001 400 mg BID for 12 weeks

Study burden and risks

Based on clinical and/or nonclinical findings, monitorable potential adverse effects of THB001 are as follows:
• Changes in hematology laboratory parameters * THB001-related hematologic effects include reductions in Red Blood Cell (RBC), reticulocytes, and White Blood cell (WBC) counts that correlate with decreased bone marrow cellularity in rats and dogs. These changes are considered on target and reversible. In the first-in-human (FiH) trial, mild reductions in mean WBC and neutrophil count were observed through 2 weeks of dosing. Mean cohort decreases in reticulocyte counts were also observed through 2 weeks of dosing.

These effects were fully reversible approximately 7 days after dosing was stopped.
• Changes in heart rate

• Changes in clinical chemistry * Colony-Stimulating Factor 1 receptor (CSF-1R) mediated inhibition of Kupffer cells may cause reduced clearance of liver function enzymes and Creatine Kinase (CK) and result in mild elevations. Prior clinical experience with targeted CSF-1R inhibitors were considered mild elevations as on target pharmacology and non-adverse (Genovese et al. 2015).
• Changes in hair color

The following potential non-monitorable effects were observed in nonclinical studies:
• Depletion of male reproductive germ cells
• Hemorrhage of corpora lutea of ovaries
• Fetal toxicity

Risks to participants in the trial will be minimized by inclusion of participants fulfilling all eligibility criteria, close clinical monitoring, individual dose stopping criteria, and dose escalation stopping criteria.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Diagnosis of chronic cold urticaria for at least 3 months.
-Participants must be refractory to antihistamine treatment.
-Participants must understand the nature of the trial and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any trial-related procedures.
-Participants currently on an antihistamine must be on a stable dose for at least 2 weeks prior to day 1 and must maintain the same stable dose throughout the treatment period.
-Positive cold stimulation test assessed by TempTest®
-Healthy as determined by the Investigator
-Men and women, age 18-75 years
-Women of child-bearing potential must not be pregnant or lactating. Women of child-bearing potential and their non-vasectomized partners must agree to use two of the following contraceptive methods during the trial and for 90 days after the (last) trial drug administration: non-hormonal intra-uterine device/system, condom, diaphragm, cervical cap with spermicide. Hormonal contraceptives may continue to be used but are not considered a highly effective form of birth control for this study.
OR Women of child-bearing potential and their vasectomized partners must agree to use one of the following contraceptive methods during the trial and for 90 days after the (last) trial drug administration: non-hormonal intra-uterine device/system, condom, diaphragm, cervical cap with spermicide. Hormonal contraceptives may continue to be used but are not considered a highly effective form of birth control for this study.
OR Women of child-bearing potential must practice sexual abstinence (when this is in line with her preferred and usual lifestyle) during the trial and for 90 days after the (last) trial drug administration.

Exclusion criteria

-Participants with acute urticaria and participants with non-cold chronic inducible urticaria.
-Current/ongoing treatment with immunosuppressant drugs, leukotriene antagonists, danazol, penicillin, angiotensin-converting inhibitors, and griseofulvin
-Any previous treatment with CDX-0159.
-A positive test for drugs of abuse at Screening.
-A positive Hepatitis B surface antigen or positive Hepatitis C or human

immunodeficiency virus (HIV) antibody result at Screening.
-Abnormal clinically significant findings on the laboratory examinations at the Screening (ALT, AST, TBL, greater than 1.5 times the upper limit of normal; Hbg, platelet count, ANC, reticulocyte count, WBC, below the lower limit of normal)
-Use of prescription or non-prescription drugs, vitamins, herbal, and dietary supplements, unless in the opinion of the Investigator and the Medical Monitor the medication will not interfere with the trial procedures or compromise participant safety.
-Received or used an investigational product (including placebo) or device within the following time period prior to the first dosing day in the current trial: 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
-A positive pregnancy test or lactation.
-A history or presence of a clinically significant hepatic, renal, gastrointestinal, cardiovascular, endocrine, pulmonary, ophthalmologic, immunologic, hematologic, dermatologic (other than chronic urticaria),or neurologic abnormality.
-A clinically significant vital signs abnormality, as judged by the principal investigator, at Screening.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-08-2022
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	THB001
Generic name:	NA

Ethics review

Approved WMO Date:	01-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-005360-21-NL
CCMO	NL81526.056.22