A Randomized, Double-Blind, Placebo-Controlled, Phase 1, Single and Multiple Ascending Dose Study to Assess the Safety, Pharmacokinetics, Pharmacodynamics, and Food Effect of THB001 in Healthy Subjects

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Part 1 - Single Ascending Dose (SAD):Primary objective:• To evaluate the safety and tolerability of single oral doses of THB001 in healthy subjects.Secondary objectives:• To characterize the plasma pharmacokinetic (PK) profile of single oral doses...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON50828

Source
ToetsingOnline

Brief title
CS0366 - THB FIH

Condition

- Other condition

Synonym
allergic asthma, and food allergy, chronic idiopathic and inducible urticaria, chronic rhinosinusitis

Health condition

allergic mediated diseases

Research involving
Human

Sponsors and support

Primary sponsor: Third Harmonic Bio
Source(s) of monetary or material Support: Third Hamonic Bio

Intervention

Keyword: food effect, pharmacodynamic, pharmacokinetic, safety

Outcome measures

Primary outcome

Part 1, Part 2 and Part 3

• Safety and tolerability parameters include: physical examination, AEs,

clinical laboratory values, vital signs and ECGs (3-lead telemetry and 12-lead

ECGs).

Secondary outcome

Part 1 and Part 2

• PK parameters for THB001 include: Cmax, tmax, t1/2, AUC0-t, AUC0-inf, CL/F

and Vz/F.

Part 1 and Part 3

Mean hourly heart rate analysis including change from baseline and placebo

corrected change from baseline (if applicable) for each subject, heart rate

nadir and time to heart rate nadir. Optional analysis of cardiodynamic

parameters including precision QT analysis may be performed.

Part 3

• PK parameters for THB001 include: Cmax, tmax, t1/2, AUC0-t, AUC0-tau,

AUC0-inf, CL/F (Day 1 only), Vz/F (Day 1 only), Cmin, Cmin,ss, CLss/F, Vss/F,

Cssavg, and AR.

Study description

Background summary

Mast cells play a central role in the pathology of allergic-mediated diseases, providing a strong rationale that depletion of mast cells can benefit patients diagnosed with allergic mucosal and cutaneous disorders in which mast cell degranulation plays a role in onset and progression. As a novel therapeutic approach, mast cell depletion should inhibit multiple mediators of symptoms of allergic diseases that have inadequate responses to single agents that target only individual mediators of mast cells or whose off-target toxicity profiles limit their use.
Mast cell activation, proliferation, and survival depend on the KIT receptor. Studies have shown that KIT mutations and kinase inhibition of mutant KIT have profound effects on mast cells. Therefore, KIT is a pharmacologically and genetically validated target to drive mast cell depletion.
THB001 is highly selective for KIT and therefore mast cell proliferation and survival. The exquisite selectivity of THB001 was demonstrated in animals by limited*to*no off*target toxicity and a defined on-target toxicity with a reasonable therapeutic window. THB001 is expected to have robust mast cell depletion and a favorable safety profile that supports clinical investigation.

Study objective

Part 1 - Single Ascending Dose (SAD):
Primary objective:
• To evaluate the safety and tolerability of single oral doses of THB001 in healthy subjects.
Secondary objectives:
• To characterize the plasma pharmacokinetic (PK) profile of single oral doses of THB001 in healthy subjects.
• To assess the effect of THB001 on ECG parameters (PR, QRS, QTcF and Heart

Rate).

Part 2 - Food Effect (FE):
Primary objective:
• To evaluate the safety and tolerability of a single oral dose of THB001 in fasted and fed state in healthy subjects.
Secondary objectives:
• To characterize the plasma PK profile of a single oral dose of THB001 in fasted and fed state in healthy subjects.

Part 3 - Multiple Ascending Dose (MAD):
Primary objective:
• To evaluate the safety and tolerability of multiple oral doses of THB001 in healthy subjects.
Secondary objectives:
• To characterize the plasma and urine PK profile of multiple oral doses of THB001 in healthy subjects.
• To assess the effect of THB001 on ECG parameters (PR, QRS, QTcF and Heart Rate).

Study design

This study is a randomized, placebo-controlled, Phase 1 study in three parts: single ascending doses (Part 1, double-blind), food effect (Part 2, open-label), and multiple ascending doses (Part 3, double-blind).
The study will be monitored by a Safety Review Committee (SRC). The intent of the SRC is to ensure that treatment does not pose undue risk to subjects. Safety, tolerability and available PK and/or PD data will be assessed by the SRC between each cohort in Part 1 and Part 3 and prior to initiation of Part 2 and Part 3.

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the IB for further information.

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

1. Subjects must understand the nature of the study and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any study-related procedures.
2. Healthy as determined by the Investigator, based on a medical evaluation including medical history, physical examination, laboratory tests and ECG recording. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if, in the opinion of the Investigator, the finding is (a) unlikely to introduce additional risk to the subject, (b) will not interfere with study procedures or confound study results, and (c) is not otherwise exclusionary (see Exclusion Criteria).
3. In Part 1 and 2, men and women aged 18-65 years (inclusive) at the time of Screening will be enrolled, and in Part 3 vasectomized men and women aged 18-65 years (inclusive) at the time of Screening will be enrolled.
4. Women of child-bearing potential must agree not to attempt to become pregnant and to use a highly effective form of hormonal (excluding oral contraceptives) or non-hormonal birth control, which entails the use of a non-hormonal intra-uterine device/system in combination with a barrier method (e.g. condom, diaphragm, cervical cap with spermicide) or abstinence during the study and for 90 days after the (last) study drug administration. Postmenopausal women must have had >=12 months of spontaneous amenorrhea (with

documented follicle-stimulating hormone (FSH) >=30 mIU/mL). Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy, or bilateral tubal ligation. Women who are surgically sterile must provide documentation of the procedure by an operative report or by ultrasound. All women must have a negative pregnancy test result on Day -1 before (first) administration of study medication.

Exclusion criteria

1. A positive urine drug screen/alcohol breath test at Screening or Day -1 of the (first) treatment period.
2. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at Screening.
3. A positive test for human immunodeficiency virus (HIV) antibody at Screening.
4. Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than the upper limit of normal (ULN) at Screening or Day -1 of the (first) treatment period. One test result up to 1.25 x the ULN is allowed. One retest at Screening and on Day -1 of the (first) treatment period is allowed. Subjects with Gilbert*s Syndrome are permitted to have total bilirubin values outside the 1.25 x the ULN, as judged by the Investigator, as long as the AST and ALT are within normal limits (WNL).

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2021
Enrollment:	108

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nap.
Generic name:	Nap.

Ethics review

Approved WMO Date:	25-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022
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

ID: 21075
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-000164-29-NL
CCMO	NL76587.056.21
OMON	NL-OMON21075

Study results

Results posted: 13-02-2023

First publication
01-02-2023