# A Phase 1, Open-Label, Fixed Sequence Drug-Drug Interaction Study to Assess the Effect of Multiple Doses of Oral THB001 on the Pharmacokinetics of Oral Caffeine, Omeprazole, and Midazolam (CYP1A2, CYP2C19 and CYP3A4 probe substrates) in Healthy Volunteers

Published: 16-12-2021
Last updated: 05-04-2024

Primary objective:• To investigate the effect of THB001 on the pharmacokinetics (PK) of caffeine, omeprazole and midazolam.Secondary objective:• To evaluate the safety and tolerability of THB001 co-administered with caffeine, omeprazole and...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51382

**Source**
ToetsingOnline

**Brief title**
CS0376-210320

### 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:** DDI, Pharmacokinetics

## Outcome measures

**Primary outcome**

PK parameters for midazolam, caffeine and omeprazole include, but are not

limited to: Cmax, tmax, AUC0-t, and AUC0-inf.

**Secondary outcome**

Safety and tolerability parameters include: physical examination, AEes,

clinical laboratory values, vital signs and 12-lead ECGs.

# 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 receptor tyrosine kinase. 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**

Primary objective:
• To investigate the effect of THB001 on the pharmacokinetics (PK) of caffeine, omeprazole and midazolam.

Secondary objective:
• To evaluate the safety and tolerability of THB001 co-administered with caffeine, omeprazole and midazolam.

Exploratory objectives:
• To determine the PK of the CYP substrate metabolites, and metabolite to parent ratios where appropriate, in the presence and absence of THB001.
• To evaluate the potential effect of genetic CYP2C19 polymorphisms on any observed variable response in the magnitude of the drug interaction between THB001 and omeprazole.

**Study design**

This is an open-label, fixed-sequence, drug-drug interaction (DDI) in healthy subjects.

One (1) dose of 400 mg THB001 , dosed in the absence and presence of 2 mg midazolam, 100 mg caffeine, and 10 mg omeprazole, is planned to be tested in 1 cohort of 18 healthy subjects.

Eligibility will be assessed during a screening period of up to 28 days. Subjects will check into the clinic one day prior to first dosing with the CYP substrates (Day -1). On Day 1, all subjects will receive midazolam, caffeine and omeprazole in a fasted state (after an overnight fast of at least 10 hours). From Day 3 up to and including Day 12, all subjects will receive a single oral dose of THB001 once daily in a fasted state (after an overnight fast of at least 10 hours). On Day 11, subjects will receive both THB001 and a second single oral doses of midazolam, caffeine, and omeprazole administered concurrently. Subjects will be released from the clinic on Day 13 after all

required study procedures are completed and if medically justified.

Subjects will return to the clinic between Day 17 and Day 19 for a follow-up visit.

Please refer to Table 5-1 for an overview of ambulatory visits and residence in the clinic.

**Intervention**

THB001 Drug Product
Caffeine (CYP1A2 substrate)
Omeprazole (CYP2C19 substrate)
Midazolam (CYP3A4 substrate)

**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. Vasectomized men and women, age 18-65 years inclusive at will be enrolled. 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. Male subjects must have had a vasectomy at least 4 months prior to the Screening Visit and must have a documented post-surgical follow up to confirm success of the vasectomy. They must also agree to use a condom from Day 1 until 90 days after the last dose of study.

## Exclusion criteria

1. A positive urine drug screen/alcohol breath test at Screening or Day -1.
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. One test result up to 1.25 x the ULN is allowed. One retest at Screening and on Day -1 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).
5. Hemoglobin, Platelet count, or White blood cell count below the lower limit of normal LLN at Screening. Hemoglobin, Platelet count, or White blood cell count below the LLN on Day -1. One retest is allowed at each visit.
6. Serum creatinine greater than the ULN at Screening or Day -1. One retest is allowed.

# Study design

## Design

**Study type:** Interventional

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 18-02-2022 |
| Enrollment: | 18 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Caffeine |
| Generic name: | caffeine |
| Product type: | Medicine |
| Brand name: | Midazolam |
| Generic name: | midazolam |
| Product type: | Medicine |
| Brand name: | Nap. |

| | |
|---|---|
| Generic name: | Nap. |
| Product type: | Medicine |
| Brand name: | Omeprazol Teva |
| Generic name: | omeprazol |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 16-12-2021 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-01-2022 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-02-2022 |
| 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

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2021-005997-25-NL |
| CCMO | NL79761.056.21 |

# Study results

Results posted: 02-03-2023

**First publication**
19-01-2023