A randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate safety, PK and the immunosuppressive effects of p38 MAPK inhibitor POLB 001 on the intradermal and intravenous LPS challenge response in healthy volunteers.

Published: 01-06-2022
Last updated: 06-04-2024

• To evaluate the effect of POLB 001 on inflammatory responses following an intradermal LPS challenge in healthy volunteers• To evaluate the effect of POLB 001 on inflammatory responses following an intravenous LPS challenge in healthy volunteers

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON51741

Source
ToetsingOnline

Brief title
Effects of p38 MAPK inhibitor POLB 001 on in vivo LPS challenge responses

Condition

- Autoimmune disorders

Synonym
inflammatory challenge study

Research involving
Human

Sponsors and support

Primary sponsor: ORPH Pharma IP Company Limited
Source(s) of monetary or material Support: ORPH Pharma IP Company Limited

Intervention

Keyword: LPS challenge, p38 MAPK inhibitor

Outcome measures

Primary outcome

• Skin response by imaging

o Perfusion by laser speckle contrast imaging

o Erythema by multispectral imaging

o Clinical score

• Blister exudate analysis

o Flow cytometry (neutrophils, monocyte subsets, T cells, B cells, NK cells and

dendritic cells)

o Cytokines (IL-6, IL-8, TNF, IL-1β)

• Skin punch biopsy (3 mm)

o Explorative analysis of MK2, HSP-27 and p38 MAPK expression by qPCR)

• Safety and tolerability

o Vital signs (HR, temperature)

o Treatment-Emergent Adverse Events

o Electrocardiography

o Haematology and chemistry blood panels

• Blood

o Cytokines (IL-6, IL-8, IL-10, TNF, IL-1β)

o Leucocyte differential

o Vascular markers (VCAM, ICAM, P-selectin, E-selectin, by 4-plex MSD)

o CRP

o P38 MAPK phosphorylation levels

• Safety and tolerability

o Vital signs (HR, temperature)

o Treatment-Emergent Adverse Events

o Electrocardiography

o Haematology and chemistry blood panels

PK serum concentration analysis of POLB 001

Ex vivo LPS response (baseline versus pre-IV LPS challenge; IL-6 and TNF)

Secondary outcome

N.a.

Study description

Background summary

Activation of the p38 mitogen activated protein kinase (MAPK) pathway drives various pro-inflammatory responses. Inhibition of the p38 pathway has been advocated as a therapeutic strategy for chronic and acute inflammatory conditions such as rheumatoid arthritis and sepsis. The synthetic compound POLB 001 is a potent and highly selective oral p38alpha/beta MAP kinase inhibitor. Poolbeg Pharma has licensed this compound, now known under code POLB 001, for further clinical evaluation. POLB 001 has previously been evaluated in a phase 1 single and multiple ascending dose study. Single doses administered were between 0.15 mg and 600 mg and multiple doses were between 30 mg and 150 mg twice a day for 6 days. No safety issues were reported across all doses

evaluated. The ex-vivo LPS assay showed a dose-dependent inhibition of TNF release after administration. In the current study, doses will not exceed the dose levels given in the previous performed MAD study. The current study will generate critically important data that adds to the existing information from the previous Phase 1 trial. Unlike the previous trial, volunteers will undergo a local (dermal LPS) and systemic (intravenous LPS) inflammatory challenge that will allow the potential effects of POLB 001 to be evaluated in-vivo.

Study objective

• To evaluate the effect of POLB 001 on inflammatory responses following an intradermal LPS challenge in healthy volunteers
• To evaluate the effect of POLB 001 on inflammatory responses following an intravenous LPS challenge in healthy volunteers

Study design

A randomized, double-blind, placebo-controlled, multiple dose, inflammatory challenge study in healthy volunteers.

Intervention

POLB 001 or matching placebo will be administered orally, twice daily, for 7 consecutive days.

Study burden and risks

Study participants will not have health benefit from study participation. This clinical study will be important to support further clinical evaluation of POLB 001 as therapeutic modality for severe acute inflammatory conditions. The study will not only generate data on the safety/tolerability of POLB 001 administration, but also provide insight into the proximal pharmacological activities of the compound, and potential dose- and time-dependent effects. This information is critical for rational dose selection for future clinical trials with POLB 001.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy male volunteers aged 18 to 55 years, inclusive. Health status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, coagulation, and urinalysis. In the case of uncertain or questionable results, tests performed during screening may be repeated to confirm eligibility or judged by the investigator to be clinically irrelevant for healthy subjects.
2. BMI in the range of 18 to 32 kg/m2, a minimum body weight of 50 kg.
3. Fitzpatrick skin type I-III.
4. Able to give written informed consent and willing to comply with all study-related procedures.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. (A history of) any clinically significant medical condition or abnormalities, as judged by the investigator.
2. History of sepsis, cardiovascular disease or malignancy.
3. History of trauma with likely damage to the spleen or surgery to spleen.
4. History of alcohol or drug abuse.

5. Any clinically significant febrile illness 30 days preceding study Day 1.
6. History of serious bleeding.
7. Clinical evidence of significant or unstable medical illness including neurological, hematological, cardiovascular (including clinically significant arrhythmia), hepatic, pulmonary, metabolic, gastrointestinal, renal, psychiatric, endocrine, or infectious diseases or malignancies. Subjects who have had splenectomy.
8. Previous participation in a systemic (i.v./inhaled) LPS challenge trial within a year before the first study day.
9. Have any current and / or recurrent pathologically, clinically significant skin condition at the lower forearms (i.e., atopic dermatitis) including tattoos.
10. Antibiotic use, operation or intervention by surgeon/dentist within one month before the first study day.
11. Subjects who have used any prescribed or non-prescribed systemic or topical medication (including herbal remedies) within 7 days of the first dose administration, or less than 5 half-lives (whichever is longer), and during the study (except for vitamin/mineral supplements) unless, in the opinion of the Investigator, the medication will not interfere with the study procedures or compromise safety.
12. Subjects who have received any medications, including St John*s Wort, known to chronically alter drug absorption or elimination processes within 30 days of the first dose administration unless, in the opinion of the Investigator, the medication will not interfere with the study procedures or compromise safety.
13. Any active inflammatory or infectious disease (e.g., periodontitis).
14. Known immunodeficiency.
15. Positive test results for Hepatitis B, Hepatitis C, HIV antibody.
16. Subjects who consume on average more than 3 units of alcohol per day (one alcohol unit =1 beer [12 oz] =1 wine [5 oz] =1 spirits [1.5 oz]) or are unable to abstain from using alcohol during the study.
17. Subjects with a positive urine drug screen/alcohol test result at screening or first admission or a history of substance abuse in the last 12 months prior to the start of the study.
18. Subjects who smoke more than 6 cigarettes or the equivalent in tobacco per day and are unwilling to abstain from smoking during the study period (from screening until EOS).
19. Loss or donation of blood over 500 mL within 3 months prior to screening or donation of plasma within 14 days prior to screening.
20. Participation in an investigational drug or device study within 3 months, or 5 half-lives whichever is longer, between last dosing in previous study and first dosing in present study or more than 4 times in the past year.
21. Any vaccination within the last 3 months; COVID19 vaccination (or time of infection) is allowed up until 2 weeks prior to the first POLB 001 /placebo dosing.
22. Intention to receive any vaccination(s) before the last day of follow-up (with the exception of vaccinations recommended for COVID19 as defined by

government vaccination guidelines).

Study design

Design

Study type:	Interventional
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):	03-08-2022
Enrollment:	36
Type:	Actual

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:	14-07-2022
Application type:	First submission
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	EUCTR2022-001458-48-NL
CCMO	NL81214.056.22