A phase 1, double-blind, randomised, placebo-controlled multiple dose study investigating the immunopharmacology of EDP1815 with multiple formulations

Published: 27-09-2018
Last updated: 15-05-2024

* To evaluate the effect of EDP1815 on the systemic immune system.* To evaluate the safety and tolerability of EDP1815 in multiple formulations.

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

Summary

ID

NL-OMON49769

Source
ToetsingOnline

Brief title
MAD immunopharmacology study of EDP1815 with multiple formulations

Condition

- Immune disorders NEC

Synonym
Auto immune diseases

Research involving
Human

Sponsors and support

Primary sponsor: Evelo Biosciences Inc.
Source(s) of monetary or material Support: Evelo Biosciences Inc.

Intervention

Keyword: Auto immune disorders, EPD1815, KLH antigen challenge, Prevotella histicola

Outcome measures

Primary outcome

* KLH challenge

o DTH after intradermal KLH re-challenge. Response characterization by Laser Speckle Contrast Imaging (LSCI) and erythema by multispectral imaging

o Serology: anti-KLH IgM and IgG

o Ex vivo lymphocyte activation upon KLH re-challenge. Response characterization by ELISPOT.

o Suction blister exudates: cytokines TNF*, IL8, IFN-*, IL6, IL-1*, IL-10, IL-33, TSLP, and immunophenotyping from cohort 2 onwards

* Whole blood ex-vivo Phytohaemagglutinin (PHA) and Lipopolysaccharide (LPS) challenges with cytokine release (LPS: TNF*, IL-6, IL-1b, IL-8, IL-2, IFN-* and IL-10. PHA: IL-2 en IFN-*) as read-out measured by MSD.

* (Changes in) regulatory T cells and B cell subsets

* Blood chemokine and cytokine levels

Secondary outcome

* Serious adverse event (SAE) and adverse event (AE) incidents

* Clinical safety laboratory measurements

* Electrocardiogram (ECG) measurements

* Vital sign measurements

* Chemistry and hematology panels

* Physical examination

* Bristol Stool Scale and stool questionnaire

* Persistent EDP1815 prevalence in stool samples

o Strain-specific PCR

* Gut microbiota composition in stool samples

o 16S RNA sequencing

* Specific markers of gastrointestinal (GI) integrity

o Faecal calprotectin (only cohort 1)

* Immune biomarkers

o Cytokines e.g. TNF-* and IL-6

o Immunoglobulins e.g. IgG (including individual subclasses IgG1 to IgG4), IgM,

IgA

* Leukocyte subsets e.g. CD3+, CD4+, CD8+, CD19+, NK-cells and CD14+

Study description

Background summary

Over the past decades evidence has emerged for an interplay between the gut microbial flora (microbiome) and the (systemic) immune system. Alteration in the composition of the gut microbiome has been associated with the presence of several (auto)inflammatory diseases. Evelo Biosciences has identified and selected individual microbial strains of human commensal bacteria based on their properties to modulate the systemic immune system to use as therapeutics for auto-immune diseases e.g. psoriasis and rheumatoid arthritis. These individual microbial strains are called monoclonal microbials. Since these monoclonal microbials are human commensal organisms they are likely to be well-tolerated and in addition are restricted to the gut when orally administered. If they are capable of modulating multiple immune pathways in humans, as different preclinical studies are suggesting, they have the potential to become an attractive therapeutic strategy in patients with (auto) inflammatory diseases, either as monotherapy or in combination with other agents.

Study objective

* To evaluate the effect of EDP1815 on the systemic immune system.
* To evaluate the safety and tolerability of EDP1815 in multiple formulations.

Study design

This is a single centre, double-blind, randomized, placebo-controlled trial to evaluate the effect of EDP1815 on the systemic immune system, using a KLH challenge. A flowchart of the study is displayed in Figure 1 below. The EDP1815 dose level to be tested is 8.0 x 10'11' total cells in each cohort (i.e. approximately 5x of the allometric scaled preclinical efficacious dose level). Participants who pass screening will be randomised either to the active (EDP1815) or placebo group. Each cohort will consist of 16 subjects, of whom 12 will receive EDP1815 and 4 will receive matching placebo. Dosing will be initiated on Day 1 and continue for 28 days, the KLH challenge will be the key pharmacodynamic endpoint.

Intervention

EPD1815

Study burden and risks

EDP1815 is a pharmaceutical preparation of a single strain of Prevotella histicola. Prevotella histicola is a commensal organism found in all human populations studied to date. EDP1815 drug-substance has viability of <0.02% and is not genetically modified.

In clinical study EDP1815-101, a total of 104 subjects including healthy volunteers and subjects with mild to moderate psoriasis and atopic dermatitis participated in Cohorts 1 * 6. Subjects were randomized to EDP1815 or placebo in a 2:1 ratio with a total of 70 subjects receiving EDP1815 in this study: 2 subjects received a single dose; 16 subjects received multiple daily doses for 14 days (healthy volunteers); 36 subjects received multiple daily doses for 28 days (psoriasis), and 16 subjects received multiple daily doses for 28 days (atopic dermatitis). Throughout this study the safety profile of EDP1815 was comparable to placebo. There have been no serious adverse events, no SUSARs, and no adverse events of severe intensity. No subjects required cessation of dosing due to an AE. Additionally, there has been no evidence of systemic absorption in the patients studied and no clinically relevant results nor trends in laboratory results.

While Prevotella is a human commensal, it is a potentially pathogenic micro-organism. Most frequently reported are urinary tract infections with a relatively mild clinical course, in most cases in immuno-compromised patients,

who are not part of the current protocol. P. histicola and EDP1815 specifically has been tested and has been found to be sensitive for various antibiotics which will be administered in the current protocol if considered necessary. The study design has been used previously in many studies, and is accepted by scientists and regulatory authorities. The first three study drug administrations per cohort will be done in the clinic under medical supervision. The subjects receiving any study drug will remain in the clinic for at least 48 hours after their first study drug administration. Thus, the subjects can be closely monitored for any adverse signs during the different treatments. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

For a structured risk assessment see Section 11 of the protocol.

Contacts

Public
Evelo Biosciences Inc.

Memorial Drive 620
Cambridge 02139 MA
US
Scientific
Evelo Biosciences Inc.

Memorial Drive 620
Cambridge 02139 MA
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Obtained prior to any screening procedures and in accordance with national, local, institutional guidelines.
2. Age * 18 years to 60 years, inclusive.
3. Participant has a body mass index of * 18 kg/m2 to * 35 kg/m2 at Screening.
4. Contraception:
a. Male participants:
* A male participant must agree to use contraception during their participation in this study and for a period of 90 days after the last dose and refrain from donating sperm during this period.
b. Female participants:
* A female participant is eligible to participate if she is not pregnant, does not plan to become pregnant, not breastfeeding, and at least 1 of the following conditions applies:
i. Not a woman of child-bearing potential (WOCBP)
OR
ii. A WOCBP who agrees to follow the contraceptive guidance during their participation in this study and for at least 3 complete menstrual cycles (*90 days) after last EDP1815 dose.
5. CRP * 10 mg/L and faecal calprotectin * 150 mcg/g faeces. Exceedings of these thresholds may be allowed by the investigator if deemed clinically irrelevant.
6. The participant has clinical laboratory evaluations (including clinical chemistry, haematology, and complete urinalysis) within the reference range for the testing laboratory, unless the results are deemed not to be clinically significant by the investigator (1 repeat test is permitted).
7. Fitzpatrick skin type I-III (Caucasian).
8. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring at Screening and on Day 1.
9. Subject needs to have sufficient space in a refrigerator to store the IMP during the ambulant dosing phase.
10. Participant has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Only subjects with a negative SARS-CoV-2 qPCR analysis prior to first dosing will be included in the study

Exclusion criteria

1. Participant has received live attenuated vaccination within 42 days prior to Screening or intends to have vaccinations during the course of the study.
2. Participant has received any investigational drug or experimental procedure within 90 days or 5 half-lives, whichever is longer, prior to study intervention administration or participant was enrolled in an investigational drug or device study within 90 days prior to first EDP1815 dosing.
3. Participant requires treatment with an anti-inflammatory drug or prophylactic antibiotics for any reason during the study period. Paracetamol will be permitted for use as an antipyretic and/or analgesic (maximum of 4 grams/day in any 24-hour period).
4. Participant has an active infection (e.g. sepsis, pneumonia, abscess) or recurrent infection, or has had an infection requiring antibiotic treatment within 42 days prior to Investigational Medicinal Product (IMP) administration.
5. Participant is diagnosed with tuberculosis (TB, as per positive skin test (Mantoux) or IFN-* release assay), or history of TB, or latent TB, or recent contact with TB (patient); having travelled to countries where TB is endemic within 56 days of planned drug administration or planning to travel to countries where TB is endemic from the moment of drug administration until 90 days after the end of the study.
6. Participant has renal or liver impairment, defined as:
a. For women, serum creatinine level * 125 *mol/L; for men, * 135 *mol/L
b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) * 1.5 x upper limit of normal (ULN), or
c. Alkaline phosphatase (ALP) and/or bilirubin > 1.5 x ULN
Exceedings of these thresholds may be allowed by the investigator if deemed clinically
irrelevant.
7. Participant has active neoplastic disease or history of neoplastic disease within 5 years of Screening (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitively treated with standard of care).
8. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
a. Unstable angina or acute myocardial infarction * 90 days prior to Screening;
b. Clinically significant heart disease (e.g. symptomatic congestive heart failure [e.g. >New York Heart Association [NYHA] Class 2]; uncontrolled arrhythmia, or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen.
9. Participant with a positive screening result for hepatitis B surface antigen, anti-hepatitis B core, hepatitis C, or HIV.
10. Participants with gastrointestinal tract disease (e.g. short bowel syndrome, diarrhoea predominant irritable bowel syndrome [IBS], celiac disease) that could interfere with the subject*s safety or pharmacodynamic effect of the monoclonal microbial.

11. Serious psychiatric or medical conditions that, in the opinion of the investigator, could interfere with treatment, compliance, or the ability to give consent.
12. The participant has a history of hypersensitivity or allergies to Prevotella (or Prevotella containing probiotics) including any associated excipients, or has a history of hypersensitivity or allergies to placebo capsule/powder (magnesium stearate, microcrystalline cellulose, colloidal silicon dioxide, hydroxypropylmethylcellulose, or mannitol) or to the hard capsule shells (hydroxyl propyl methyl cellulose and titanium dioxide), or has a known allergy against Alhydrogel®.
13. Participant has a history of Schistosomiasis (infection with Schistosoma parasite).
14. The participant has taken any over-the-counter (OTC) medication (with the exception of paracetamol and anti-histamines) within 14 days prior to Baseline (Day -1) or any prescription medications or nutraceuticals (e.g. supplements including high doses of probiotics and prebiotics, as usually found in capsules/tablets/powders) within 28 days prior to Baseline (Day -1) or anticipates an inability to abstain from these products for the duration of the study period. Note that probiotic and prebiotic foods e.g. yoghurts that contain low doses are allowed.
15. The participant uses probiotic capsules within 14 days prior to screening.
16. The participant has a significant history of drug abuse or regular use of illicit drugs or a history of alcohol abuse within 1 year prior to Screening.
17. The participant uses more than 10 cigarettes per day and/or is unable to refrain from cigarettes or tobacco use or other nicotine-containing products (e.g., patches) during 4 consecutive days.
18. The participant has donated more than 400 mL of blood or blood products within 90 days prior to Baseline (Day -1) or plans to donate blood during the study.
19. The participant has a diastolic blood pressure *50 or *90 mm Hg, or a systolic blood pressure *105 or *140 mm Hg at Screening or Baseline (Day -1) unless deemed to be not clinically significant by the investigator.
20. The participant has had an acute, clinically significant illness or major surgery within 30 days prior to screening.

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):	27-12-2019
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EDP1815
Generic name:	N.A.
Product type:	Medicine
Brand name:	IMMUCOTHEL

Ethics review

Approved WMO Date:	27-09-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	08-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2020
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: 20845
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-002658-65-NL
CCMO	NL67464.056.18
Other	NL8676
OMON	NL-OMON20845