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A study to evaluate the immune response after administration of lipopolysaccharide (LPS) in the skin of healthy volunteers

Submission date 08/11/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 09/11/2023	**Overall study status** Completed	
Last Edited 24/02/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
The purpose of this study is to measure how the complement system, which is part of the immune system, is activated after injecting a substance called LPS that causes inflammation when injected into the skin of healthy people. We want to use this as a way to test new drugs that target the complement system in the future. We will also look at how other molecules in the skin change after LPS injection and how the complement system is activated in the blood outside the body. We will use different methods to collect and analyze the data, such as measuring the redness and blood flow of the skin, taking small samples of the skin and examining them for complement and other molecules using special techniques, and measuring the levels of complement and other molecules in the blood.

Who can participate?
Healthy, male and female, volunteers between 18 and 45 years

What does the study involve?
Twelve people (six men and six women) will get a small amount of LPS injected into their skin, and then have small pieces of skin taken from the injection site at different times: before the injection, and 1, 3, 6, 9, and 24 hours after the injection. The study will only last for 24 hours because the reaction to LPS is short and limited to the injection site, so there is no need to check on the participants after that.

What are the possible benefits and risks of participating?
This study will not provide any medical benefit to the people who participate in it. The study involves taking small samples of skin tissue, called skin punch biopsies. These samples are needed to examine a part of the immune system, called complement, that can only be seen under a microscope. The biopsies are done with a tiny tool that makes a 3mm hole in the skin. The hole is so small that it does not require any stitches. People who have darker skin types (from IV to VI on the Fitzpatrick scale) are more likely to develop scars or bumps on the skin after a biopsy, so they are not eligible for this study.

Where is the study run from?
The Centre for Human Drug Research, Leiden (the Netherlands)

When is the study starting and how long is it expected to run for?
July 2023 to March 2024

Who is funding the study?
The Centre for Human Drug Research, Leiden (the Netherlands)

Who is the main contact?
Juliette van den Noort, clintrials@chdr.nl

Contact information

Type(s)
Public

Contact name
Miss Juliette van den Noort

ORCID ID
https://orcid.org/0000-0001-7356-6847

Contact details
Zernikedreef 8
Leiden
Netherlands
2333 CL
31 71 5246 400
clintrials@chdr.nl

Type(s)
Scientific, Principal investigator

Contact name
Mr Matthijs Moerland

ORCID ID
https://orcid.org/0000-0002-8064-8426

Contact details
Zernikedreef 8
Leiden
Netherlands
2333 CL
+ 31 71 5246 400
clintrials@chdr.nl

Additional identifiers

Protocol serial number
CHDR2346

Study information

Scientific Title
An intradermal LPS challenge study to evaluate local complement activation in healthy volunteers

Study objectives
Inflammation is a response to damaged tissue and/or pathogens resulting in cellular activation and a release of cytokines. Although inflammation is in principle a healthy process, in some cases an excessive and/or poorly regulated inflammatory response can be harmful to the host, which is the case in many inflammatory disorders. Hyperactivation of the complement system can be a driver of a variety of autoimmune and inflammatory diseases. Therefore, investigational products are under development for regulation of complement. An in vivo complement activation model would be of great benefit for the early clinical evaluation of the pharmacological activity of novel complement-targeting investigational compounds, but such a model is not readily available.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/11/2023, Stichting BEBO (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 592-405 871; info@stbebo.nl), ref: NL85105.056.23

Primary study design
Observational

Study design
Single-center observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Regulation of the complement system

Interventions
Subjects will arrive at the clinic on day one. LPS will be administered at 5 locations on the back after which skin biopsies will be taken at different times. Additionally, images of the skin will be made at these timepoints using Laser Speckle Contrast Imaging and Antera 3D photography. Blood will be collected to assess the ex vivo complement response. On D2, one additional biopsy will be taken and skin-images will be made, after which subjects will be discharged. There will be no follow-up.

Intervention Type
Other

Primary outcome(s)
For local complement activation/depositions after intradermal LPS challenge, histology and/or immunofluorescence may be used for complement proteins in biopsy material. Biopsies will be taken predose and at 1, 3, 6, 9 and 12h post dose.

Key secondary outcome(s)
1. For local biomarkers after intradermal LPS challenge, immunohistochemistry and/or qPCR and /or RNA sequencing and/or protein-bases assessments will be used. Biopsies will be taken predose and at 1,3,6,9 and 12h post dose.
2. For ex vivo complement activation by LPS, blood-based analysis of complement proteins will be used. Blood will be collected predose.

Completion date
31/03/2024

Eligibility

Key inclusion criteria
1. Healthy male and female subjects, 18 to 45 years of age, inclusive. Healthy 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, blood serology, coagulation and urinalysis. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
2. Body mass index (BMI) between 18 and 30 kg/m² and a minimum weight of 50 kg, inclusive;
3. Fitzpatrick skin type I-III (Caucasian);
4. Subjects and their partners of childbearing potential must use effective contraception for the duration of the study. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:
4.1. Post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy;
4.2. Post-hysterectomy.
5. Able and willing to give written informed consent and to comply with the study restrictions.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex

All

Key exclusion criteria

1. History of pathological scar formation (keloid, hypertrophic scar) or keloids or surgical scars in the target treatment area of the upper back that in the opinion of the investigator, would limit or interfere with dosing and/or measurement in the trial;
2. Have any current and / or recurrent pathologically, clinical significant skin condition at the treatment area (i.e. atopic dermatitis); including tattoos;
3. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
4. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrolment or planned to use during the course of the study;
5. Use of topical medication (prescription or over-the-counter [OTC]) within 30 days of study drug administration, or less than 5 half-lives (whichever is longer) in local treatment area
6. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year.
7. Loss or donation of blood over 500 mL within three months prior to screening or donation of plasma within 14 days of screening
8. Any history or current presence of a (medical) condition that would, in the opinion of the investigator, potentially compromise the safety or compliance of the patient or may preclude the patient's successful completion of the clinical trial.
9. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening.
10. Abnormal findings in the resting ECG at screening defined as:
10.1 QTcF> 450 or < 300 ms for men and QTcF> 470 or < 300 ms for women;
10.2 Notable resting bradycardia (HR<45 bpm) or tachycardia (HR>100 bpm);
10.3 Personal or family history of congenital long QT syndrome or sudden death;
10.4 ECG with QRS and/or T wave judged to be unfavorable for a consistently accurate
10.5 QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
10.6 Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
11. Chronic infection with HIV, hepatitis B (HBV) or hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test at screening excludes a subject.
12. Presence of current or a history of ongoing, chronic or recurrent infections or infectiousdisease. Exception for plantar warts and onychomycosis.
13. (History of) autoimmune disease, such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis or other immune-inflammatory diseases.
14. Hypersensitivity for dermatological marker at screening.
15. Current smoker and/or regular user of other nicotine-containing products (e.g., patches).
16. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.
17. Use of any prescription or OTC medications within 7 days or 5 half-lives (whichever is longer) prior to LPS administration, unless, in the opinion of the Investigator, the medication will not interfere with the study procedures or compromise safety. Exception for prescription contraceptives and paracetamol in case of local pain.
18. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days prior to

LPSadministration(s), or within less than 5 half-lives (whichever is longer), until the end of study.
19. Any vaccination within the last 4 weeks before day 1 or intention to receive any vaccination (s) before the end of study.
20. Person of childbearing potential who is pregnant, breast-feeding, or planning to become pregnant during the study.
21. Prolonged exposure of the investigational skin (back) to sunlight (including artificial tanning) from three weeks prior to the study until EOS.

Date of first enrolment
09/11/2023

Date of final enrolment
16/01/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
The Centre for Human Drug Research
Zernikedreef 8
Leiden
Netherlands
2333 CL

Sponsor information

Organisation
Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication