A study in healthy volunteers to evaluate the effect of repeated LPS skin challenges in a single individual

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Primary Objectives* To evaluate the safety and tolerability of repeated intradermal LPS challenges in healthy volunteers* To evaluate the local response in healthy volunteers after repeated intradermal LPS challenges performed 14 days apartSecondary...

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

Summary

ID

NL-OMON55995

Source
ToetsingOnline

Brief title
Effect of repeated local LPS challenges in healthy volunteers

Condition

- Other condition

Synonym
Challenge

Health condition

Challenge model development

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd

Intervention

Keyword: Intradermal, LPS, Safety, Tolerability

Outcome measures

Primary outcome

>Safety:

* Treatment-emergent (serious) adverse events ((S)AEs)

* Safety labs tests (acute phase proteins (CRP), leukocyte differentiation)

* Vital signs (HR, BP)

* NRS pain score

>Dermal imaging/scoring:

* Perfusion by Laser speckle contrast imaging (LSCI)

* Erythema by Antera 3D camera

* Erythema grading score

>Blister exudate analysis

* Neutrophils and monocyte subsets

Secondary outcome

>Dermal imaging/scoring

* Perfusion

* Erythema

Study description

Background summary

Lipopolysaccharide (LPS) is a pro-inflammatory substance found on the outer cell membranes of Gram-negative bacteria. It protects these bacteria from phagocytosis and lysis. LPS is recognized by Toll-like receptor (TLR) 4 in a normally functioning immune system. Administration of LPS into healthy human volunteers creates a model in which immune responses can be monitored and influenced. LPS can be administered via intravenous, inhaled, nasal and intradermal routes. Intradermal administration creates a rapid, limited local inflammatory reaction which allows detailed insights into the local immune response (CHDR1752A, CHDR1752B, CHDR1912B, CHDR2136). In previous intradermal LPS studies at CHDR, LPS was applied on the lower forearm.

To date, intradermal LPS studies testing the ability of investigational medicinal products (IMPs) to reduce inflammation at the challenge site have used a parallel control group, with each subject challenged with LPS only at a single time point after dosing of placebo or active drug. Consequently, to generate dose response information for the pharmacodynamic effect of an IMP on the LPS induced inflammation, different subjects must be used for the placebo and each different dose level. An alternative design would be to challenge subjects with LPS at baseline before administration of the IMP, and then repeat the LPS challenge at a different skin site after dosing the IMP, such that each subject becomes its own control. It can be envisaged that subsequent to the second LPS challenge, a subject would be dosed again with a higher dose level of IMP and then after a defined time period rechallenged with LPS to again measure pharmacodynamic effects. This uptitration design would enable a single subject to be used as a control, low IMP dose and high IMP dose to measure the effects on LPS-induced inflammation, potentially reducing the number of subjects for a study by a factor of 3. An additional potential benefit of the uptitration design is reduced overall variability.

In this study, we aim to assess the safety of repeated local LPS challenges and to investigate if immune tolerance to LPS occurs in the skin. The latter will be assessed by the recruitment of monocytes and neutrophils to sites of an intradermal LPS challenge performed at D1, D15 and D29. Additionally, to enable the proposed follow-up study design with uptitration of an IMP, the response will need to be assessed at six different administration sites. Therefore, in this study, participants will receive multiple intradermal LPS injections on the upper back over time. Subjects will receive one additional injection in the lower arm, to assess the difference in clinical response between the lower arm and the upper back. This design permits studying the response to repeated intradermal LPS within one participant, as well as comparison of the response between intradermal LPS applied on the lower arm and the upper back. If a

similar immune response is seen at the D1, D15 and D29 timepoints, future IMP studies would then be able to implement this design such that each subject would act as its own control and could also be used to ascertain dose-response relationship.

Study objective

Primary Objectives
* To evaluate the safety and tolerability of repeated intradermal LPS challenges in healthy volunteers
* To evaluate the local response in healthy volunteers after repeated intradermal LPS challenges performed 14 days apart

Secondary Objectives
* To compare local inflammatory responses to LPS in skin on volar forearm and the back

Study design

This is a single-centre, repeated LPS challenge study to explore the effects of local intradermal LPS challenges over time in healthy volunteers. A total of 8 subjects receive 7 intradermal LPS injections each (1 on the volar forearm and 6 on the upper back) for non-invasive imaging and to measure monocyte infiltration via suction blistering on the back.

Intervention

LPS, purified lipopolysaccharide prepared from Escherichia Coli: 113: H10:K negative (U.S. Standard Reference Endotoxin)

Study burden and risks

Although subjects do not have any direct medical benefit from participating in the study, LPS has been administered safely to humans over 30 years, and is generally well tolerated. This study, however, may provide futures studies with an investigational medicinal product (IMP) an uptitration design to enable a single subject to be used as a control, low IMP dose and high IMP dose to measure the effects on LPS-induced inflammation. Consequently reducing the number of subjects for a study potentially. An additional benefit of the uptitration design is reduced overall variability.

In this study, all subjects will receive 7 intradermal LPS injections (5 ng per injection) in total with a maximum of 3 injections per study day. LPS has been widely used as a challenge agent to induce mild and reversible inflammation. In the study of Basran et al. (2013), subjects received intradermal LPS injections with a dose up to 15 ng per injection (maximum dose of 45 ng per subject in

total). This led to a small skin reaction with mild erythema and edema. No significant adverse effects of intradermal LPS administration were observed.

CHDR has conducted several studies (CHDR1752A, CHDR1752B, CHDR1912B, CHDR2124, CHDR2136, and CHDR2149) using the intradermal LPS challenge model to induce a local, mild, and transient skin reaction. Subjects received up to 4 injections in total with a dose of 5 ng per injection. No systemic side effects were observed. However, a slight transient rise in circulating leukocytes (mainly neutrophils) following intradermal LPS administration was observed in some of the subjects, but declined to baseline levels with-in 48h. Administration of intradermal LPS has shown to be safe and well-tolerated. Although the total LPS dose administered in this study will be higher than in previous studies conducted at CHDR (35 ng in total, divided over 3 dosing days), it is expected that repeated exposure to LPS will not result in additional safety issues, as the LPS response is local and transient, and there will be no repeated exposure on the same application site. Additionally, the maximum dose administered per day will be lower than in the previous CHDR study5, with a total of 15 ng LPS on day 1, and 10 ng LPS on day 15 and 29. Additionally, the LPS dose injected (5 ng per injection) is much lower than the dose used in i.v. LPS challenge studies6,7

The invasive measurement in this study consists of blister formation. This will be limited to 6 blisters per subject. To minimize the risk of post inflammatory hyperpigmentation, Fitzpatrick skin types 4-6 are excluded.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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 and urinalysis. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment 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 of childbearing potential must use effective contraception for the duration of the study;
5. Able and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

1. History of pathological scar formation (keloid, hypertrophic scar) or keloids or surgical scars in the target treatment area (lower arm and 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 (lower arm and upper back, i.e. atopic dermatitis); including tattoos;
3. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrolment or planned to use during the course of the study;
4. Known immunodeficiency
5. Use of topical medication (prescription or over-the-counter [OTC]) in local treatment area or any medication that may interfere with the study objectives as judged by the investigator within 30 days of study drug administration, or less than 5 half-lives (whichever is longer)
6. Participation in an investigational drug or device study within 3 months, or

5 half-lives whichever is longer, prior to screening or more than 4 times in the past 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 (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. Pregnant, a positive pregnancy test, intending to become pregnant during the study conduct, or breastfeeding.
10. Positive hepatitis B surface antigen (HbsAg), hepatitis C antibody (HCV ab), or human immunodeficiency virus antibody (HIV ab) at screening.
11. A history of ongoing, chronic or recurrent infectious disease
12. Hypersensitivity for dermatological marker at screening
13. Current smoker and/or regular user of other nicotine-containing products (e.g., patches)
14. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen.
15. Presence of current, clinically relevant infections
16. Any vaccination within the last 4 weeks before day 1. Intention to receive any vaccination(s) before the last day of follow-up.
17.Prolonged exposure of the investigational skin (lower arm, back) to sunlight (including artificial tanning)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2023
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	02-11-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2023
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
CCMO	NL84863.056.23