CIT013 First in Human study

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Objectives Part A: • To evaluate the safety and tolerability of CIT-013 after administration of single, ascending, IV doses in healthy volunteers. • To evaluate the pharmacokinetics of CIT-013 after administration of single, ascending, IV doses in...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24009

Bron
Nationaal Trial Register

Verkorte titel
CITRYLL001

Aandoening

Acute and chronic inflammatory disorders, Autoimmune disorders

Ondersteuning

Primaire sponsor: Citryll BV
Overige ondersteuning: Citryll BV

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

• Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit

Toelichting onderzoek

Achtergrond van het onderzoek

*Summary Neutrophils, the most abundant type of leukocytes in human blood, contribute to the first line of defence and use their extensive armoury
to protect the host against infection. Neutrophils kill microbes via phagocytosis, the generation of reactive oxygen species, or the release
of their granular content. A more recently described antimicrobial function is the formation of neutrophil extracellular traps (NETs). NETs trap and efficiently eliminate pathogens and have been shown to protect mice and humans against bacterial and fungal infections. In spite of their importance in host defence, aberrant and prolonged NET release is associated with the pathophysiology of many acute and chronic inflammatory disorders. In particular, incomplete clearance of NETs contributes to vascular injury, which could lead to tissue damage and organ failure, or even death. NETs have been shown to block tissue repair signals, leading to impaired wound healing in diabetes, while activation of the clotting system by NETs occludes blood vessels in thrombosis. In addition, antimicrobial proteins and histones that are present in NETs are highly cytotoxic and induce endothelial dysfunction in systemic lupus erythematosus (SLE), vasculitis, and sepsis. Furthermore, NETs are a source of autoantigens and trigger autoimmunity, which is associated with the production of autoantibodies against various NET components in rheumatoid arthritis (RA), small-vessel vasculitis (SVV) antiphospholipid syndrome (APS) and SLE.
Several stimuli (e.g. microbes, cytokines, immune complexes) can initiate NET formation by binding to neutrophil receptors which activate the endoplasmic reticulum to release stored calcium ions. When this happens nuclear and granular membranes disintegrate, the chromatin decondenses and diffuses into the cytoplasm, where it mixes with cytoplasmic proteins. Citrullination of histones by protein arginine deiminase 4 (PAD4) as well as enzymatic degradation of nucleosomes by neutrophil elastase (NE) and Myeloperoxidase (MPO) enhances further chromatin decondensation. Finally, the cell-membrane breaks owing to the pressure exerted
by the expanding chromatin, and the NET decorated with antimicrobial proteins and toxic histones is released into the extracellular space. Formed NETs are deposited in inflamed tissue but can also be found in the blood circulation during inflammation. Since the above-described process of NET formation is only happening in cases of microbial and sterile inflammation, it is near to absent in healthy individuals. If NETs appear in a healthy individual, they will readily be degraded by desoxyribonucleases. Citryll’s clinical development candidate CIT-013 is a first in class humanized monoclonal antibody, a so called therapeutic anti-citrullinated protein
antibody (tACPA), that targets NET biology and its pathological effects. As a consequence, CIT-013’s targets (NETs containing citrullinated histones) are not present in healthy individuals. For this reason, in part B of the study, healthy volunteers are challenged with i.v. lipopolysaccharides (LPS) which causes a temporary inflammatory response and the induction of NETs. CIT-013’s effect on these inflammatory responses as well as its NET inhibitory and clearance effect will be studied.

Doel van het onderzoek

Objectives Part A:
• To evaluate the safety and tolerability of CIT-013 after administration of single, ascending, IV doses in healthy volunteers.
• To evaluate the pharmacokinetics of CIT-013 after administration of single, ascending, IV doses in healthy volunteers.

Objectives Part B:
• To evaluate the safety and tolerability of CIT-013 after administration of single, ascending, IV doses in LPS challenged healthy volunteers.
• To evaluate the pharmacokinetics of CIT-013 after administration of single, ascending, IV doses in LPS challenged healthy volunteers.
• To evaluate the pharmacodynamic effects of CIT-013 by characterizing the inflammatory response after administration of single, ascending, IV doses in LPS challenged healthy volunteers.

Onderzoeksopzet

Day -42 (Screening) till EOS at week 12

Onderzoeksproduct en/of interventie

CIT-013
placebo

Contactpersonen

Publiek

Citryll
Leonie Middelink

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Wetenschappelijk

Citryll
Leonie Middelink

0613328444

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Healthy men or women of non-child bearing potential (WNCBP), 18 to 55 years of age (inclusive) at screening. The health status is verified by absence of evidence of any clinically significant active or uncontrolled chronic disease following a detailed medical history, a complete physical examination including vital signs, laboratory measurements, and 12-lead ECG;
2. Signed informed consent, able and willing to comply with the requirements of the study protocol.
3. Body mass index (BMI) between 18 and 32 kg/m2, inclusive, and a body weight between 50 and 150 kg, inclusive at screening.
4. All male volunteers must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Any confirmed or suspected disease or condition associated with immune system impairment, including autoimmune diseases, HIV, asplenia or recurrent severe infections.
2. Use of chronic (more than 14 days) immunosuppressant or immunomodulatory drugs within the 3 months prior to IMP administration, or isolated (non-chronic) use within 30 days prior to IMP administration.
3. Subject has an active, uncontrolled acute or chronic systemic fungal, bacterial, and/or viral, infection within the past 30 days.
4. Subjects with evidence or history of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases.
5. Subject has a positive SARS-CoV-2 PCR based test within 72 hours of receiving CIT-013.
6. Use of prescription or over-the-counter (OTC) drugs, vitamins, minerals and dietary supplements, within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication until EOS. Herbal supplements
7. and hormone replacement therapy must be discontinued 30 days prior to the first dose of study medication until EOS. Excluded from this list is paracetamol at doses of <4 g/day on all study days except day 1 of part B.
8. Exceptions will only be made if the rationale is clearly documented by the investigator.
9. Receipt of live or attenuated vaccine 90 days prior to first study intervention administration.
10. Vaccination (completion of 2nd vaccination shot if applicable) against SARS-CoV-2 or

influenza vaccinations less than 14 days prior to first study drug administration.
11. Known hypersensitivity to any of the constituents or excipients of CIT-013 or history of relevant drug and/or food allergy (anaphylactic, anaphylactoid reactions).
12. Smoking > than 10 cigarettes (or equivalent) per week and/or using nicotine-based products within 1 month prior to CIT-013 administration and/or unwillingness to abstain from the use of these from screening until EOS.
13. Extreme exercise (e.g. marathon or triathlon) within 2 weeks of screening.
14. Subject has participated in an intravenous LPS challenge study before (Part B).

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	26-07-2021
Aantal proefpersonen:	52
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Toelichting
No deidentified individual clinical trial participant-level data (IPD) will be shared in the near future.

Ethische beoordeling

Positief advies

Datum:	07-09-2021

Soort: Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 56333
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9747
CCMO	NL77528.056.21
OMON	NL-OMON56333

Resultaten