A randomized, double-blind, placebo-controlled single and multiple ascending dose study to test the safety, tolerability, pharmacokinetics and pharmacodynamics of NT-0167 in healthy volunteers

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Primary:- To evaluate the safety and tolerability of NT-0167 in healthy volunteersSecondary:- To evaluate the pharmacokinetic (PK) profile of NT-0167 in healthy volunteers after the administration of single ascending (SAD) and multiple ascending...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49667

Source
ToetsingOnline

Brief title
SAD and MAD of NT-0167 in healthy volunteers

Condition

- Other condition

Synonym
inflammatory disorders; neurodegenerative diseases

Health condition

inflammatory disorders and neurodegenerative diseases

Research involving
Human

Sponsors and support

Primary sponsor: NodThera
Source(s) of monetary or material Support: Nodthera

Intervention

Keyword: Inflammation, NT-0167, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

Tolerability / safety endpoints

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

* Clinical laboratory tests

o Haematology

o Chemistry

o Urinalysis

o Coagulation

o Thyroid function tests

* Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

o Respiratory Rate (breaths/min)

* Electrocardiogram (ECG)

o Heart Rate (HR) (bpm), PR-, QRS-, and QTcF-intervals

o Morphological abnormalities

* Holter ECG (not in Food cohort)

* Physical examination

* Weight (only during MAD cohorts)

Pharmacokinetic endpoints

* AUCinf, AUClast, CL/F, Cmax, t1/2, tlag, tmax, Vz/F

Pharmacodynamic endpoints

* Inflammasome-driven cytokines in whole blood challenge assay:

o IL-1*

o IL-18

o IL-6

o TNF

Secondary outcome

N.A.

Study description

Background summary

Inflammasomes are large multiprotein complexes which play a key role in innate immunity by participating in the production of the pro-inflammatory cytokines interleukin-1* (IL-1*) and IL-18 [Guo et al, 2016]. These related cytokines cause a wide variety of biological effects associated with infection, inflammation and autoimmune processes. They are both produced as inactive precursors, pro-IL-1* and pro-IL-18, and share a common maturation mechanism that requires caspase-1. Caspase-1 itself is synthesized as a zymogen, pro-caspase-1, that undergoes autocatalytic processing resulting in two subunits that form the active caspase-1. Activation of caspase-1 occurs within the inflammasome following its assembly.

The best characterised inflammasome is the NLRP3 (NOD-, LRR- and pyrin domain containing protein 3; also known as NALP3 and cryopyrin) inflammasome. It comprises the NLR protein NLRP3, the adapter ASC (apoptosis-related speck-like protein) and pro-caspase-1. The general consensus is that maturation and release of IL-1* requires two distinct signals: the first signal leads to synthesis of pro-IL-1* and other components of the inflammasome, such as NLRP3 itself; the second signal results in the assembly of the NLRP3 inflammasome, caspase-1 activation and IL-1* maturation and secretion.

Activation of the NRLP3 inflammasome can be triggered by numerous stimuli which may be chemically and structurally very different. Triggering molecules (pathogen-associated molecular patterns, PAMPs), such as bacterial lipopolysaccharide and fungal zymosan, can activate the NLRP3 inflammasome and induce IL-1* secretion in the presence of adenosine triphosphate (ATP) [Guo et al, 2016]. Besides PAMPs, the NLRP3 inflammasome can be activated by molecules associated with stress or danger, including crystalline and particulate substance (danger-associated molecular patterns, or DAMPs).

NLRP3 inflammasome activation inhibitors are being developed for the treatment of a range of inflammatory disorders including CAPS, NASH, inflammatory bowel disease and neurodegenerative diseases (e.g. Alzheimer*s disease and Parkinson*s disease). Clinical evidence through IL-1* modulation, NLRP3 gain-of-function mutation-driven diseases and non-clinical evidence through genetic manipulation and pharmacological inhibition suggests that efficacy can be achieved across a range of chronic diseases by inhibition of NLRP3 inflammasome activation. CP-456,773 [Dostert et al, 2009], a prototype molecule originally discovered by Pfizer in the 1990s and subsequently shown to be an NLRP3 inflammasome inhibitor in 2015 [Primiano et al, 2016] provides additional clinical proof of concept as this molecule was progressed to a Phase II rheumatoid arthritis study and showed evidence of a pharmacodynamic response. Nodthera is developing a small molecule inhibitor of NLRP3, preventing the assembly of the inflammasome. This compound, NT-0167, is a differentiated molecule from the Pfizer compound CP-456,773. NT-0167 is a potent and selective NLRP3 inflammasome inhibitor in LPS/ATP stimulated human peripheral blood mononuclear cells and human blood, compared to CP-456,773, NT-0167 shows a considerable improvement in human blood activity due to reduced plasma protein binding. It shows efficacy in a single dose acute LPS/ATP mouse model and in an MSU-mediated air-pouch inflammation model in mice inducing a decrease in IL-1* compared to control, indicating inhibition of the inflammasome. To describe the human target coverage for NT-0167, a PK/PD model was built based on the available mouse and human PK/PD data with CP-456,773. According to this model, the dose that is predicted to give 80% target coverage of NT-0167 at trough is 200mg QD or 100mg BID, which is projected to achieve a Cmax of 4584ng/mL (9.96uM total; 158ng/mL (0.69µM free) and AUCt of 71429ng.h/mL (155.3µM.h total; 4929ng.h/mL (10.7µM.h free). NT-0167 had no effect on hemodynamic or ECG parameters or body temperature, compared with vehicle controls treatments in a conscious minipig study at doses up to 300mg/kg. NT-0167 had no measurable

impact on behavioural or physiological parameters in the Irwin rat study up to 1000mg/kg. In a conscious rat respiratory study, NT-0167 did not induce test article-related changes in any of the respiratory parameters measured up to 1000mg/kg. NT-0167 showed no liability for QT prolongation in a GLP-compliant hERG study with 3% inhibition at 30 µM. In the GLP-compliant 28-day rat study following dosing of NT-0167, the no observed adverse effect level (NOAEL) was 1000 mg/kg/day, the mean combined (male and female) Cmax value at Day 22 was 459 ug/mL and the AUC0-t value was 3490 ug·h/mL (representing a 48-fold safety margin over the projected AUCt at 200mg QD). In the GLP-compliant 28-day minipig study following dosing of NT-0167, the no observed adverse effect level (NOAEL) was 1000 mg/kg/day, the mean combined (male and female) Cmax value at Day 22 was 122 ug/mL and the AUC0-t value was 605 ug·h/mL (representing a 8.5-fold safety margin over the projected AUCt at 200mg QD).
The current first-in-human study will evaluate the safety/tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of NT-0167 in healthy volunteers.

Study objective

Primary:
- To evaluate the safety and tolerability of NT-0167 in healthy volunteers
Secondary:
- To evaluate the pharmacokinetic (PK) profile of NT-0167 in healthy volunteers after the administration of single ascending (SAD) and multiple ascending doses (MAD);
- To evaluate the pharmacodynamic (PD) properties of NT-0167 in healthy volunteers after single ascending and multiple ascending doses based on ex vivo inflammasome challenges;
- To evaluate the effect of food on the PK profile and tolerability of NT-0167 after a single dose administration.

Study design

This study comprises up to 6 randomized, double-blind, placebo-controlled, SAD cohorts, and up to 4 randomized, double-blind, placebo-controlled, MAD cohorts. Each cohort will consist of 8 subjects: 2 subjects will receive placebo and 6 will receive active NT-0167. Before starting the MAD cohorts, an assessment of the effect of food intake on the PK of the Investigational Medicinal Product (IMP) will be studied in the subjects from one of the SAD cohorts.

Intervention

NT-0167

SAD: 10 - 2000 mg
Food cohort: 300/1000/2000 mg

MAD: 100 mg - 200 mg

Study burden and risks

The pharmacological and toxicological profile of NT-0167 observed in pre-clinical studies suggest that administration to humans in a carefully monitored study is acceptable. As with any new investigational product, the administration of NT-0167 may be associated with unforeseen and serious risks. Intense clinical monitoring will therefore be employed to ensure subject safety. In addition to this, risks to participating volunteers will be minimised by the strict adherence to inclusion and exclusion criteria, gradual dose escalation, and the implementation of study and dose escalation pausing rules which may lead to stopping the study.
The study design has been used previously in many entry-into-man studies and is accepted by scientists and regulatory authorities. All study drug administrations 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 each 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening:
1. Signed informed consent and willing and able to comply with the study protocol;
2. Healthy men or women of non-child bearing potential (WONCBP), 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;
3. Female subjects must be of non-childbearing potential in accordance with one of the following definitions:
* Surgically sterile (by hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy) as documented by a surgical report or by ultrasound, or
* Post-menopausal (age-appropriate spontaneous amenorrhoea for *12 months and follicle-stimulating hormone (FSH) * 40 IU/mL together with the absence of oral contraceptive use for >12 months);
4. Male volunteers agree to use barrier protection when they engage in sexual relations with women of child-bearing potential (WOCBP) or lactating women for the duration of their participation in the study and until 90 days after EOS.
5. Body mass index (BMI) between 18 and 32 kg/m2, inclusive, and with a minimum bodyweight of 50 kg;
6. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.
7. Have the intention to be reachable by mobile phone or e-mail during the whole study period

Exclusion criteria

Eligible subjects must not meet any of the following exclusion criteria at screening or pre-dose:
1. Lactating females;
2. Female volunteers with a positive pregnancy test at screening or baseline prior to IMP administration;
3. Evidence (including symptoms, physical signs, and/or laboratory values) of any active or chronic disease or condition that could interfere with, or for

which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator;
4. Any confirmed or suspected disease or condition associated with immune system impairment, including auto-immune diseases, HIV, asplenia or recurrent severe infections.
5. Use of chronic (more than 14 days) immunosuppressant or immunomodulatory drugs within the 6 months prior to IMP administration, or isolated (non-chronic) use within 30 days prior to IMP administration;
6. Any history of severe allergic reaction(s);
7. Any confirmed significant drug hypersensitivity reactions (including skin reactions or anaphylaxis), or known allergies (non-active hay fever is acceptable);
8. History of clinically significant systemic disorders including haematological, renal, endocrine, gastrointestinal, hepatic, cardiovascular, pulmonary, dermatological and neurological disorders, or other conditions which could interfere with the interpretation of the study results or compromise the health of the volunteers;
9. Any history of psychiatric condition that may affect participation in the study or preclude compliance with the protocol;
25. Receipt of any vaccination with 3 months of IMP administration.
26. Participation in an investigational drug, vaccine or device study within 3 months prior to first dosing or plans to participant in other investigational drug, vaccine or device research during the study period.
27. Previous participation in a study with an investigational drug or device involving the dosing of a biological targeted at any immune pathway within one year prior to screening;
38. Any other known factor, condition, or disease that, in the opinion of the Investigator, might interfere with treatment compliance, study conduct or interpretation of the results, or may compromise volunteer safety.

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:	Completed
Start date (anticipated):	31-01-2020
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NT-0167
Generic name:	N.a.

Ethics review

Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-04-2020
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: 23660
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-004228-39-NL
CCMO	NL72337.056.19

Study results

Date completed: 30-09-2020

Results posted: 12-04-2021

First publication
01-01-1900