A randomized, double-blind, placebo-controlled PK/PD guided, phase I study in healthy volunteers given escalating, single intravenous doses of NI-0101 in the absence or presence of a systemic LPS challenge.

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Part 1:- To assess tolerability, safety and PK of escalating single Intravenous (IV) doses of NI-0101 in healthy volunteers with the aim of covering a wide range of plasma concentrations up to those theoretically reflecting a potential therapeutic...

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

Summary

ID

NL-OMON37163

Source
ToetsingOnline

Brief title
Phase 1 NI-0101-01.

Condition

- Autoimmune disorders
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Rheumatoid arthritis.

Research involving
Human

Sponsors and support

Primary sponsor: Novimmune S.A.
Source(s) of monetary or material Support: Pharmaceutical Industry.

Intervention

Keyword: Pharmacodynamics, Pharmacokinetics, Safety., TLR4 inhibition

Outcome measures

Primary outcome

Part 1:

Laboratory parameters: standard blood haematology and biochemistry tests,

urinalysis;

Incidence and severity of Adverse Events with particular focus on Infusion

Related Reactions and Infections;

Pharmacokinetic profile of NI-0101;

Pharmacodynamic effects of NI-0101 by means of ex vivo challenges for the

assessment of the MyD88 (e.g. TNF*, IL-6) and TRIF (e.g. IFN*, IFN* or IP-10)

pathways;

Immunogenicity of NI-0101, i.e. the presence of anti-NI 0101antibodies.

Part 2:

Incidence and severity of Adverse Events;

Laboratory parameters: standard blood haematology and biochemistry tests,

urinalysis;

Pharmacokinetic profile of NI-0101;

Pharmacodynamic effects of NI-0101 by means of an in vivo LPS challenge by the biomarker assessment of the MyD88 (e.g. TNF*, IL-6) and TRIF (e.g. IFN*, IFN* or IP-10) pathways;

Effects of NI-0101 on the LPS induced inflammation and systemic response (e.g. body temperature, CRP).

Immunogenicity of NI-0101, i.e. the presence of anti-NI 0101antibodies.

Secondary outcome

N.A.

Study description

Background summary

NI-0101 is a humanized immunoglobulin gamma (IgG)1 kappa (*) monoclonal antibody (mAb) that binds and antagonizes TLR4. NI-0101 binds with high affinity (dissociation constant, Kd = 139 pM), independently of MD-2 (myeloid differentiation factor-2). NI-0101 prevents TLR4 dimerization and, thus, ligand driven receptor-mediated intracellular signalling. Two amino acid substitutions, introduced within the SKAF motif of the Fc-domain of NI-0101, destroy the binding sites for interactions with Fc*RIII and the complement component, C1q, while maintaining the binding to Fc*RI and to Fc*RII. Polymorphisms for the Fc*RIIa will affect the potency of NI-0101 for blocking TLR4-mediated cytokine release (half maximum inhibitory concentrations, IC50s of 128, 223, 2191 pM for genotype 131R/R, 131R/H and 131H/H, respectively, with distribution of the genotypes of 21%, 46%, and 33%, respectively).
Using NI-0101 and a murine NI-0101 surrogate (5E3), the role of TLR4 activation in the pathogenesis and progression of RA has been further corroborated in a number of experiments performed by NovImmune. Examples of these are the in vivo experiments in murine animal models of RA (i.e. collagen-induced arthritis, CIA and IL-1Rn-/- models) using 5E3 and the studies to investigate the effect of NI-0101 in blocking the spontaneous production of inflammatory cytokines by synovial tissue explants obtained from RA patients.
NI-0101 provides a novel and unique means of inhibiting the TLR4-mediated inflammatory response and thus appears to be an attractive agent to blunt the inflammatory response in diseases like RA, where inflammation initiated by TLR4 plays a critical role in the pathophysiology of the disease.

Study objective

Part 1:
- To assess tolerability, safety and PK of escalating single Intravenous (IV) doses of NI-0101 in healthy volunteers with the aim of covering a wide range of plasma concentrations up to those theoretically reflecting a potential therapeutic effect on inflamed tissues;
- To determine the PD effects of NI-0101 by an ex vivo whole blood challenge with an exogenous TLR4 ligand (LPS) and, optionally, an endogenous ligand, as a proof of mechanism;
- To determine the potential impact of Fc*RIIA polymorphism on NI-0101 effects;
- To investigate immunogenicity of NI-0101, i.e. the presence of anti-drug antibodies (ADAs).

Part 2:
- To assess the tolerability, safety , pharmacodynamic effects and PK of escalating single IV doses of NI-0101 in healthy volunteers exposed to an in vivo LPS challenge;
- To describe the dose-concentration-inhibition relationship of in vivo and ex vivo LPS challenges performed at the end of NI-0101 infusions;
- To demonstrate that the above described relationships hold with time after NI-0101 administration;
- To investigate immunogenicity of NI-0101, i.e. the presence of anti-drug antibodies.

Study design

Randomized, double-blind, placebo-controlled, PK/PD guided, single ascending dose interventional Phase I study.

Part 1: assessment of effects using whole blood ex vivo stimulations (LPS and optionally an endogenous ligand).
Part 2: assessment of effects using an in vivo challenge with LPS.

Intervention

A single intravenous infusion of NI-0101 or placebo without (Part 1) or with (Part 2) an in vivo LPS challenge.

NI-0101 is a humanized immunoglobulin gamma (IgG1) kappa monoclonal antibody (mAb) that blocks both the signal transduction pathways of the trans-membrane protein, human Toll-Like Receptor 4 (TLR-4). The matched placebo is a sterile solution for intravenous infusion that is identical to the NI-0101 drug product but does not include the active substance. LPS (lipopolysaccharide) is an endotoxin frequently used in human research.

Study burden and risks

TLR4 signalling is essential in host defense and excessive and long-lasting inhibition is associated with impaired host defense. Although there is a theoretical chance that this may occur in the trial, it is unlikely as the trial is designed so that excessive and long-lasting inhibition of TLR4 signalling is unlikely to occur. The dose of NI-0101 will not exceed a predefined threshold of residual cytokine levels for adequate immunity against microbial threat. It is considered that problems can be adequately managed in case of serious adverse events calamity as CHDR is closely linked to Leiden University Medical Center.
Determination of a safe starting dose was achieved by combining classical methods and the MABEL approach using data on the in-vitro inhibition of the compound assessed in human blood. Dose-escalation for dosing next cohorts will only be performed after consensus by the Principle Investigator, the sponsor and -if needed- external experts (Safety Review Committee) that this is safe to proceed to the next dose level.

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

Healthy male and female volunteers; Signed the informed consent prior to any study related procedure; aged between 18 and 40 years (inclusive); BMI between 18 and 30 kg/m2 (inclusive);
known genotype for the Fc*RIIa receptor;

Exclusion criteria

Clinically significant abnormalities; pregncy or breast feeding; susceptibility for infections and/or immunocompromised state and/or latent TB; sepsis in history;

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):	20-11-2012
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	25-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2012-003657-28-NL
CCMO	NL41750.018.12