A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)

Published: 28-11-2018
Last updated: 27-12-2024

Primary Objectives: - To evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for EOS-HDFN. - To evaluate the efficacy of nipocalimab as measured by proportion of patients with live birth at or...

Ethical review	Approved WMO
Status	Completed
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON52622

Source
ToetsingOnline

Brief title
nipocalimab Injection

Condition

- Red blood cell disorders
- Blood and lymphatic system disorders congenital

- Abortions and stillbirth

Synonym
fetal blood-disorder

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag International, NV
Source(s) of monetary or material Support: Janssen-Cilag International NV

Intervention

Keyword: Blood disorder, Hematolic disease of Fetus and Newborn, Maternal alloantibody, Phase II

Outcome measures

Primary outcome

Safety:

Maternal nipocalimab safety and tolerability will be evaluated in terms of the incidence and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interests (AESIs) (ie, infections requiring use of anti-infectives [oral or intravenous (IV) antibacterial/antiviral/antifungal], and hypoalbuminemia >= Grade 3 according to the Common Terminology Criteria for Adverse Events v 5.0 [CTCAE]) in the mother. Additional safety assessments will include 12-lead electrocardiogram (ECG) parameters, clinical laboratory tests (chemistry, hematology, urinalysis), analysis of anti-nipocalimab antibody levels, vital signs, physical examinations, and use of concomitant medications and therapies in the mother. Mothers will be followed for safety for 24 weeks post-delivery. Adverse events, SAEs, and AESIs will be analyzed by frequency, severity, and relationship to study therapy. Although

nipocalimab is not expected to be transmitted to maternal breast milk in clinically meaningful quantities, colostrum/breast milk samples will be collected for an exploratory analysis to determine if nipocalimab is present.
Fetal health will be assessed by frequent ultrasound assessments (at least every 2 weeks) and umbilical and uterine artery Doppler measurements of flow velocity will be initiated if fetal biometry indicates the potential for intrauterine growth restriction. In addition, surveillance of fetal heart rate before, during, and after nipocalimab infusion will be done.
For the neonates, AEs and concomitant medication/therapies/procedures will be collected from birth through postnatal Month 6 (Week 24). Serious AEs, AESIs (ie, infections requiring use of anti-infectives [oral or IV antibacterial/antiviral/antifungal] and unexpected/unusual childhood illnesses), and pediatric neurodevelopment will be monitored through Week 96 (~the first 2 years of age). Other safety assessments include postnatal safety laboratory assessments (chemistry and hematology); immune development (IgG, lymphocyte phenotyping); vital signs; physical examination findings (including growth); and use of concomitant medications and therapies (including number of intravenous immunoglobulin [IVIG] doses given). Although nipocalimab is not expected to cross the placenta, an analysis of potential effects of exposure to nipocalimab on the neonate/infant will include evaluation of the following: fetal (where possible, if cordocentesis is performed) and neonatal nipocalimab concentrations (from cord blood sample obtained at birth and at Week 4 after birth) and FcRn receptor occupancy (RO).

Efficacy:

The primary efficacy endpoint is the proportion of patients with live birth at or after GA Week 32 and without an IUT throughout their pregnancy.

Secondary outcome

Efficacy:

- Percentage of patients with live birth
- Percentage of patients at GA Week 24 without an IUT
- Gestational age at first IUT
- Number of IUTs required
- Percentage of patients with fetal hydrops
- Percentage of neonates requiring phototherapy
- Percentage of neonates requiring exchange transfusions
- Number of days of phototherapy required by neonate

Percentage of neonates requiring simple transfusions in the first 12 weeks of life

- Number of simple transfusions required by neonate in the first 12 weeks of life

PD

• Maternal FcRn RO and levels of IgG and alloantibodies

PK

- Serum PK profile of nipocalimab in maternal patients

Exploratory Endpoints:

- Fetal hemoglobin, hematocrit, alloantibody and bilirubin levels at first IUT and in subsequent IUTs

- Maternal serum levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE •

- Presence of nipocalimab in colostrum/breast milk

- Placental evaluation

- Neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, hematocrit, IgG, and alloantibodies, FcRn RO (all measured from cord blood at birth)

- Peak bilirubin levels during the neonatal period

- Number of IVIG doses received by neonate

- Slope of middle cerebral artery peak systolic velocity (MCA-PSV) by Doppler ultrasound

Study description

Background summary

HDFN is a rare and potentially life-threatening condition in which maternal alloantibodies cross the placenta during pregnancy and bind to fetal red blood cells (RBCs) thereby causing RBC destruction and anemia in the fetus. In current standard of care practice, intrauterine transfusions (IUT) are performed with risk of early fetal demise. There is an unmet medical need for an effective nonsurgical intervention for pregnant mothers with HDFN, especially for those that are likely to require an IUT during early gestation (e.g. prior to 24 weeks gestation) when the procedure*s risk of fetal loss is relatively high. Nipocalimab is intended to reduce the risk and severity of fetal anemia by reducing the transfer of maternal IgG to the fetus.

Study objective

Primary Objectives:

- To evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for EOS-HDFN.
- To evaluate the efficacy of nipocalimab as measured by proportion of patients with live birth at or after gestational age (GA) 32 weeks and without intrauterine transfusion (IUT) throughout their entire pregnancy.

Secondary Objectives:
- To evaluate the efficacy of nipocalimab on antenatal management and outcome as measured by GA at first fetal IUT, frequency of fetal IUT, and frequency of live birth.
- To evaluate the efficacy of nipocalimab on postnatal management and outcome as measured by severity of hyperbilirubinemia, phototherapy, exchange transfusions, and simple transfusions in the first 12 weeks of life.
- To evaluate the PD activity of nipocalimab as measured by effects on maternal FcRn occupancy, and maternal and neonatal/infant levels of total IgG and alloantibodies.
- To evaluate the PK of nipocalimab.

Study design

This is a Phase 2, multicenter, open-label study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of nipocalimab (M281), a fully human effectorless monoclonal antibody against the neonatal Fc receptor (FcRn), in pregnant women at high risk for early onset severe (EOS)-HDFN. Blockade of FcRn by nipocalimab is intended to reduce the risk and severity of fetal anemia by reducing the transfer of maternal immunoglobulin (Ig)G, including pathogenic alloantibodies, to the fetus, and by blocking FcRn-mediated (IgG) recycling, thereby reducing pathogenic antibody in maternal circulation.

Intervention

Nipocalimab will be administered once weekly (QW) by IV infusion at a dose of 45 mg/kg. The 45 mg/kg dose will be calculated every 2 weeks using the patient*s weight measured at the visits indicated in the SOE rounded to the nearest 0.1 kilogram. The maximum dose amount given in any patient at any dosing visit should not exceed 5.4 grams (ie, assuming a body weight of no greater than 120 kg). Infusion duration and post infusion observation period are as specified in the Infusion Manual. Each pregnant woman in the study will receive nipocalimab treatment for approximately 20 weeks (~20 infusions); no reference therapy will be administered. Refer to the SOE Section 1.3 in protocol, for timing of dose administration. If a patient requires an IUT during the study, nipocalimab administration must be stopped

Study burden and risks

Description of and risks associated with nipocalimab administration:
- Infection-nipocalimab may cause a lowering in the level of antibodies in the patient*s blood. Since antibodies fight infection, there may be increased risk of infection while you are receiving nipocalimab and for about a month after nipocalimab is discontinued. Since vaccines work by generating antibodies, their effectiveness may be decreased by nipocalimab. Nipocalimab also prevents the patient*s antibodies from crossing into the fetus. Therefore there may be increased risk of infection in the first months of the baby*s life.
- Possibility of severe allergic reaction and infusion-related reaction
- Swelling, itching or infection at the site of infusion
- Swelling- nipocalimab will likely cause a lowering in the level of albumin (a protein in the human blood) in the patient*s blood. A lowering of albumin increases the risk of edema (swelling).
- In pregnant monkeys placental injury (infarcts) has occurred in some animals. Although the relevance to human mothers is unknown, fetal growth will be monitored throughout the pregnancy. If there is evidence of unusually slow fetal growth, treatment with nipocalimab will be stopped.
- Babies who are breast fed could ingest nipocalimab through breast milk causing an increased risk of infection due to lower IgG levels in the baby.

Description of and risks associated with study procedures:
12-Lead Electrocardiogram (ECG): * Skin irritation at the electrodes application site.
Blood draws: pain, bruising at the point where blood is taken, redness and swelling of the vein and infection,fainting.

IVIG (Intravenous immunoglobulin) administration - The most common risks include:
• headache
• flushing
• chills
• fever
• muscle pain
• wheezing
• high heart rate
• lower back pain
• nausea
• vomiting
• low blood pressure
• rashes including hives
• rare but serious adverse reactions have been reported in newborns including severe allergic reactions, kidney failure, abnormal blood tests, and colitis.

Vaccin Influenza:
• soreness, redness, or swelling where the shot was given
• cough

• fever
• aches
• headache
• itching
• fatigue

Vaccin Pneumococcal
• Injection site reactions
• muscle or joint aches or pain
• fever
• chills
• headache
• nausea
• vomiting
• stiffness of the arm or the leg where the vaccine was injected

Vaccin TdAP:
• Pain where the shot was given
• Redness or swelling where the shot was given
• Mild fever of at least 100.4°F
• Headache
• Tiredness
• Nausea, vomiting, diarrhea, stomach ache
• Chills, sore joints
• Body aches
• Rash, swollen glands

Many procedures that are completed in the study are considered Standard of Care (SOC) which means that the patient are likely to undergo these procedure regardless of whether the patient is in the study or not. Any SOC procedures that will be done during the study may also carry some risks. These procedures are described in the ICF appendix D.

Contacts

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BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in the study:
1. Able to understand and voluntarily provide written informed consent to participate in the study.
2. Female and >=18 years of age.
3. Pregnant to an estimated GA of 8 up to 14 weeks.
4. A previous pregnancy with a gestation that included at least one of the following at <=24 weeks gestation:
a. Severe fetal anemia, defined as hemoglobin <=0.55 multiples of the median (MoM) for GA (see table in Protocol v6.0 18Dec2019, page 55).
b. Fetal hydrops (ascites) with an MCA-PSV MoM >=1.5
c. Stillbirth with fetal or placental pathology indicative of HDFN
5. Maternal alloantibody titers for anti-D of >=32, or anti-Kell titers >=8.
6. Free fetal deoxyribonucleic acid (DNA) consistent with an antigen positive fetus (blood sample drawn from the mother).
7. Maternal evidence for immunity to measles mumps, rubella, and varicella, as documented by serologies performed during Screening. If initial serologies are borderline or negative, they may be repeated at a second lab. Alternatively, vaccination records can be used to support evidence of immunity.
8. Screening IgG and albumin levels within the laboratory normal ranges.
9. Willing to receive standard of care with IUT if clinically indicated.
10. Agree to receive recommended vaccinations per local standard of care for both mother and child throughout the course of the study.
11. Willing to forego collection of cord blood for stem cell storage or other non-study purposes.

12. For mother and neonate, willing to forego participation in another clinical trial of an investigational therapy for the duration of their participation in the current study.
13. Willing to consent to a 24-week safety follow-up period for the patient and a 96-week safety follow-up period for the neonate/infant.
14. It is recommended that patients are up-to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study patients who received locally-approved (and including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for pregnant women receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment.

Exclusion criteria

Exclusion Criteria:
Patients who meet any of the following criteria will be excluded from the study:
1. Currently pregnant with multiples (twins or more).
2. Pre-eclampsia in current pregnancy or history of pre-eclampsia in a previous pregnancy.
3. Gestational hypertension in the current pregnancy.
4. Current unstable hypertension
5. History of severe or recurrent pyelonephritis; or 4 or more lower urinary tract infections in the past year or in a previous pregnancy, or genital herpes.
6. History of genital herpes infection
7. History of atypical mycobacterial disease or herpes zoster infection within the last 6 months.
8. History of malignancy (except treated basal cell carcinoma of the skin) with or without systemic cancer chemotherapy.
9. Positive for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C during Screening.
10. Presence of any of the following during Screening: clinically significant abnormal hematologic laboratory values, creatinine > 1.5 x upper limit normal (ULN), or clinically significant abnormal ECG reflective of heart disease.
11. Active infection at Screening or Baseline with Coxsackie, syphilis, cytomegalovirus, toxoplasmosis or herpes simplex 1 or 2, as evidenced by clinical signs and symptoms (evidence for prior infection or exposure, but without clinical signs and symptoms of active infection is acceptable).
12. Active infection with tuberculosis as evidenced by positive QuantiFERON-TB testing.
13. Immunosuppression because of underlying medical condition, including:
* History of hereditary or congenital immunodeficiencies, cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia

* History of solid organ or bone marrow transplantation
* Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject, require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results
14. Requires treatment with corticosteroids or immunosuppression for disorders unrelated to the pregnancy (use of low-potency topical corticosteroids or intra-articular corticosteroids is permitted).
15. History of drug allergy, hypersensitivity, or intolerance to any drug product that, in the opinion of the Investigator, would compromise the safety of the patient.
16. In the Investigator*s opinion, shows evidence of ongoing alcohol/substance abuse/dependence.
17. Smoking during pregnancy.
18. Received plasmapheresis and/or IVIG during the current pregnancy for treatment of HDFN.
19. Has received or is expected to receive any live virus or bacterial vaccine within 12 weeks prior to screening or has a known need to receive a live vaccine while receiving nipocalimab, or within 12 weeks after the last administration of nipocalimab in the study or has received Bacille Calmett-Guérin (BCG) vaccine within 1 year prior to the first administration of nipocalimab.
20. Currently receiving an antibody-based drug or an Fc-fusion protein drug
21. Received an investigational drug and/or device within 30 days or 5 half-lives prior to receiving the first IV infusion of nipocalimab.
22. Received nipocalimab in a prior clinical trial
23. A history or presence of clinically significant cardiovascular, pulmonary, hepatic (eg, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease), renal, hematologic, gastrointestinal, endocrine/metabolic, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or severe or recurrent infections (eg, frequent hospitalized pneumonia), or any other condition or issue that, in the opinion of the Investigator, would jeopardize the safety of the patient or fetus/neonate/infant or the validity of the study results.
24. History of myocardial infarction, unstable ischemic heart disease, or stroke.
25. COVID-19 infection: During the 6 weeks prior to baseline (regardless of vaccination status), have had ANY of:
(a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR
(b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR
(c) close contact with a person with known or suspected SARS-CoV-2 infection
Exception: may be included with a documented negative result for a validated SARSCoV-2 test:
- obtained at least 2 weeks after conditions (a), (b), (c) above (timed

from resolution of key clinical features if present, eg fever, cough, dyspnea) AND
- with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-06-2019
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nipocalimab
Generic name:	n.a.

Ethics review

Approved WMO

Date:	28-11-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	26-02-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-10-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2017-004958-42-NL
CCMO	NL67367.000.18