An Open-Label Uncontrolled Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Activity of Nipocalimab in Children Aged 2 to less than 18 years with Generalized Myasthenia Gravis

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This study has been transitioned to CTIS with ID 2022-502539-21-00 check the CTIS register for the current data. The purpose of this study is to determine the effect of nipocalimab on total serum immunoglobulin G (IgG) in pediatric participants 2 to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON51698

Source
ToetsingOnline

Brief title
A Study of Nipocalimab in Children with Myasthenia Gravis

Condition

- Neuromuscular disorders

Synonym
Generalized Myasthenia gravis, Myasthenia Gravis

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: The sponsor of the study: Janssen-Cilag International

Intervention

Keyword: Myasthenia Gravis, Pediatrics

Outcome measures

Primary outcome

• The effect of nipocalimab on total serum IgG in pediatric participants 2 to <18 years of age with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy.

• The safety and tolerability of treatment with nipocalimab in pediatric participants 2 to <18 years of age with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy.

• The pharmacokinetics of nipocalimab in pediatric participants 2 to <18 years of age with gMG who have an insufficient clinical response to ongoing, stable standard of care therapy. All primary PK and IgG endpoints will be summarized descriptively over time for the evaluable population, and for each age cohort (2 to < 12, or 12 to < 18 years old).

Secondary outcome

• The activity of nipocalimab in gMG as measured by the change from baseline in Myasthenia Gravis - Activities of Daily Living (MG-ADL) efficacy score

• The activity of nipocalimab in gMG as measured by the change from baseline in Quantitative Myasthenia Gravis (QMG) efficacy score

• The effect on quality of life as measured by the European Quality of Life 5-Dimension Youth (EQ-5D-Y) tool

• The effect on fatigue as measured by the Neurological Quality of Life (Neuro-QoL) pediatric fatigue score. All secondary endpoints will be summarized descriptively over time for the evaluable population, and for each age cohort (2 to < 12, or 12 to < 18 years old).

Exploratory Endpoints

• The relationship between nipocalimab dose, nipocalimab PK, total serum IgG, MG-ADL score and QMG score as assessed by a PK-PD model.

• The effect of nipocalimab treatment on autoantibody levels (anti-AChR and anti-MuSK)

• The effect on health-related quality of life as measured by the Pediatric Quality of Life Inventory (PedsQL)

Study description

Background summary

Myasthenia gravis in the pediatric population is classified into three categories: 1) transient neonatal myasthenia, 2) juvenile myasthenia gravis (juvenile MG) and 3) congenital myasthenic syndromes (CMS). Juvenile MG is an autoimmune disorder in which autoantibodies to structural components of the neuromuscular junction disrupt neuromuscular transmission. Similar to adults, the most common presentation in all juvenile MG is ocular muscle weakness, usually accompanied by ptosis
Disease progression from ocular MG to the more severe gMG, which includes additional skeletal muscle involvement, occurs in roughly 80% of adult patients. Lower rates have been described in all pediatric subsets and particularly in prepubertal children. Within the juvenile MG population, 23% to 43% of postpubertal (>12 years of age) patients progress to generalized MG compared to only 8% to 15% of prepubertal patients. This study is being performed to determine if the treatment of pediatric gMG with IV nipocalimab

will lead to a reduction in total serum IgG concentration.

Study objective

This study has been transitioned to CTIS with ID 2022-502539-21-00 check the CTIS register for the current data.

The purpose of this study is to determine the effect of nipocalimab on total serum immunoglobulin G (IgG) in pediatric participants 2 to less than (<) 18 years of age, the safety and tolerability of treatment with nipocalimab in children and adolescents and to evaluate the pharmacokinetics (PK) of nipocalimab in children and adolescents with generalized myasthenia gravis (gMG) who have an insufficient clinical response to ongoing, stable standard-of-care therapy.

Study design

This is a Phase 2/3, multicenter, open-label, uncontrolled, interventional study to evaluate pharmacokinetics, pharmacodynamics, safety, and activity of intravenous nipocalimab, administered in addition to protocol-allowed, stable, standard-of-care therapy for the treatment of gMG in pediatric participants from 2 to <18 years of age.

The study will consist of a screening period, a 24-week Active treatment Phase, and a Long-term Extension (LTE) Phase that will be of variable duration per participating country, depending on the timing of market authorization and commercial availability of nipocalimab. The Active treatment Phase will be comprised of 2 cohorts: Cohort 1 and Cohort 2. Cohort 1 will include adolescent gMG participants aged 12 to <18 years of age. After the Active treatment Phase is completed for Cohort 1, Cohort 2 (participant children with gMG aged 2 to <12 years of age) will be enrolled and receive nipocalimab for 24 weeks. Participants who early terminate or permanently discontinue study intervention prior to Week 24 of the Active treatment Phase will be replaced to ensure at least 6 participants in each cohort will complete the Week 24 visit. After completion of the Active treatment Phase, all participants from Cohorts 1 and 2 will have the option to enroll in an LTE phase. Participants who do not enroll in the LTE at the completion of the Active treatment Phase will complete a Safety Follow-up Visit after their last infusion of study intervention.

Intervention

Participants aged 2 to less than [<] 18 years of age will receive nipocalimab once every two weeks for 24 weeks. After Week 24, all participants will have the option to enroll in long term extension (LTE).

Study burden and risks

All possible side effects and risks related to nipocalimab are not known.
Problems that are not expected may arise and they may be life-threatening. Some may be serious and may require treatment or additional testing.
Based on the limited experience in healthy individuals and patients and our current understanding of how nipocalimab might work in the body, there are several types of side effects that might occur in people receiving nipocalimab.
These effects include the following:
Infections, Lowering of albumin in the blood, Placental Infarction in pregnant women receiving nipocalimab, Low antibodies in babies born to pregnant mothers receiving nipocalimab, Increases in lipids
Vaccinations
Nipocalimab lowers the level of all antibodies in the blood, including the antibodies your body generates in response to a vaccine. The effectiveness of vaccines may be decreased while you are receiving nipocalimab and for a few weeks after the last dose of the study drug.

Blood collections
The subject might get a bruise or irritation at the place where the needle goes into his/her skin. Some patients may faint and, in rare cases, can get an infection.
For cohort 1 (adolescents 12 to <18 years of age): about 269 mL of blood in total will be collected during the Screening and Active Treatment Phases, and 264 mL of blood in total during the LTE.
For cohort 2 (children 2 to <12 years of age): about 181 mL of blood in total will be collected during the Screening and Active Treatment Periods, and 179 mL during the LTE.
LTE blood volumes are estimated for a period of 2 years.

Rituximab may increase the risk of infection. If you have been treated with rituximab in the past, rituximab may also increase the risk of infection long after you receive your last dose.
Since both nipocalimab and rituximab may have an increased risk of infection during the study. If you have ever been treated with rituximab, you should discuss this with the investigator.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Boy or girl 2 to <18 years of age.
2. Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for gMG as defined by the MGFA Clinical Classification Class IIa/b, IIIa/b, or IVa/b at screening
3. Has a positive serologic test for acetylcholine receptor (anti-AChR) antibodies or muscle-specific tyrosine kinase (anti-MuSK) antibodies at screening.
4. Has suboptimal response to current stable therapy for gMG according to the investigator. Stable therapy is defined as the following, as applicable to their specific therapy(ies):
a. If taking an acetylcholinesterase inhibitor, the participant must have been on a stable dose and regimen for at least 2 weeks prior to screening. Changes to the dose of
acetylcholinesterase inhibitors may be permitted if medically necessary during any phase of the trial.
b. If taking a glucocorticosteroid, the participant must have been on a stable dose and regimen for at least 4 weeks prior to baseline.
c. If currently receiving immunosuppressants, the participant must have been on the given immunosuppressant for >=6 months and on a stable dose for >=3 months prior to
baseline. Allowed concomitant immunosuppressants are azathioprine,

mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.
OR
Has discontinued corticosteroids and/or immunosuppressants/immunomodulators including eculizumab or other novel approved immune agents at least 4 weeks prior to screening due to intolerance or lack of efficacy.

Note: All above background medications must be optimized and unchanged for the duration specified in Criteria #4 prior to screening and/or baseline visits. Investigators are encouraged to consider all treatment escalation options, including thymectomy, prior to enrolling. Participants started on new treatments must meet the above stable dose duration rules, and cannot meet exclusion criterion #6 as defined in Section 5.2.

5. A participant using herbal, naturopathic, traditional Chinese remedies, ayurvedic or nutritional supplements, or medical marijuana (with a doctor*s prescription) is eligible if the use of these medications is acceptable to the Investigator. These remedies must remain at a stable dose and regimen throughout the study
6. Participants who have undergone splenectomy (if local regulatory authority has not requested exclusion of participants with splenectomy) must be at least 3 months post resection prior to screening and must be vaccinated as per the United States Center for Disease Control and
Prevention annual Recommended Immunization Schedule for Ages 18 years or younger, United States. (www.cdc.gov) OR must be vaccinated as per territory-specific guidelines or local regulations.
Note: This criterion is not applicable if splenectomy is excluded by the local authority.
7. Has sufficient venous access to allow drug administration by infusion and blood sampling as per the protocol.
8. Is recommended to be up to date on all age-appropriate vaccinations (eg diphtheria and tetanus) prior to screening as per routine local medical guidelines. It is strongly recommended that participants, as applicable, will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen and it should be at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment. (see also Section 6.8.3).

Weight
9. Participants should have a body weight and body mass index between 5th and 95th percentile for age and sex. Obese participants greater than 95th percentile and underweight participants below 5th percentile may participate following medical clearance.

Sex and Contraceptive/Barrier Requirements

10. Criterion removed per Amendment 1.
11. A female of childbearing potential must have a negative highly sensitive serum (*-human chorionic gonadotropin [*-hCG]) at Screening and a negative urine pregnancy test at Day 1 prior to administration of study intervention.
12. A female must be (as defined in Section 10.6, Appendix 6: Contraceptive and Barrier Guidance.)
a. Not of childbearing potential, or
b. Of childbearing potential and
Sexual abstinence is strongly recommended; however heterosexually active female participants must practice a highly effective, preferably user independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study intervention and until 30 days after last dose
- the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.6, Appendix 6: Contraceptive and Barrier Guidance.
Note: Labeling requirements of concomitant treatment a participant is currently receiving
will supersede if more stringent.
13. Female participants of childbearing potential must agree not to donate or freeze eggs (ova,
oocytes), for future use for the purposes of assisted reproduction, during the study and for
a period of 30 days after the administration of study intervention.
14. 14.1 Sexual abstinence is strongly recommended; however, heterosexually active
post-pubertal male participants must wear a condom when engaging in any activity that
allows for passage of ejaculate to another person during the study and for at least 90 days
after receiving the last administration of study intervention. In addition, male participants
with partners who are females of childbearing potential are highly encouraged to inform
their partner to use highly effective contraception methods that result in a low failure rate
(less than 1% per year). See Section 10.6, Appendix 6: Contraceptive and Barrier Guidance.
15. A post-pubertal male participant must agree not to donate sperm for the purpose of
reproduction during the study and for a minimum 90 days after receiving the last administration of study intervention.

Informed Consent
16. A legal guardian (as defined in Section 2. Introduction) must sign an

informed consent
form (ICF) indicating that he or she understands the purpose of, and procedures required
for, the study and is willing to participate in the study. Parent(s) (preferably both if
available or as per local requirements) [(or their legally acceptable representative)] must
sign an ICF indicating that he or she understands the purpose of, and procedures required
for, the study and is willing to allow the child to participate in the study. Assent is also
required of children capable of understanding the nature of the study (typically 7 years of
age and older) as described in Section 10.4.3, Appendix 4: Regulatory, Ethical, and Study
Oversight Considerations
17. A legal guardian or primary caregiver must be available to help the study-site personnel
ensure follow-up; accompany the participant to the study site on each assessment day
according to the SoA; consistently and consecutively be available to provide information
on the participant using the rating scales during the scheduled study visits.

Exclusion criteria

1. Has a history of severe and/or uncontrolled hepatic (eg, viral/alcoholic/autoimmune
hepatitis/cirrhosis and/or metabolic liver disease), gastrointestinal, renal, pulmonary,
cardiovascular (including congenital heart diseases), psychiatric, neurological
musculoskeletal disorder, any other medical disorder(s) (eg, diabetes mellitus), or
clinically significant abnormalities in screening laboratory, that might interfere with
participant's full participation in the study, and/or might jeopardize the safety of the
participant or the validity of the study results.
Note: Any condition for which, in the opinion of the investigator, participation would
not be in the best interest of the participants (eg, compromise well-being) or that could
prevent, limit, or confound the protocol-specified assessments.
2. 3.1 Has MGFA Class I disease or presence of MG crisis (MGFA Class V) at screening,

history of MG crisis within 1 month of screening, or fixed weakness (and/or *burnt out* MG). (Note: Participants should not be actively deteriorating at the screening or baseline visit such that they meet the criteria for Clinical Deterioration as defined in Section 6.8.2).
3. Has MGFA Class I disease or presence of MG crisis (MGFA Class V) at screening, history of MG crisis within 1 month of screening, or fixed weakness (and/or *burnt out* MG).
Note: Participants should not be actively deteriorating at the screening or baseline visit such that they meet the criteria for Clinical Deterioration as defined in Section 6.8.2.
4. Is dependent on gastric tube for nutritional needs or is ventilator-dependent.
5. Is actively undergoing radiation or chemotherapy for an unresected thymoma/malignant thymoma. Participants with stable, benign thymoma (stage I or IIa, for example) for which no treatment has been undertaken in the past 3 years may be allowed following discussion with the sponsor*s medical monitor.
6. Has had a thymectomy within 12 months prior to screening, or thymectomy is planned during the Active treatment Phase of the study.
7. Has current or a history of any neurologic disorder other than MG that might interfere with the accuracy of study assessments, including but not limited to any chronic neurodegenerative disease, altered level of consciousness, dementia, abnormal mental status, major congenital neurologic defect, Lambert-Eaton myasthenic syndrome, drug induced MG, or hereditary forms of myasthenic syndrome.
8. Currently has a malignancy or has a history of malignancy within 3 years before screening (with the exception of localized basal cell carcinoma and/or squamous cell carcinoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention administration).

9. Has known allergies, hypersensitivity, or intolerance to nipocalimab or its excipients
(refer to the IB).
10. Has shown a previous severe immediate hypersensitivity reaction, such as anaphylaxis
to therapeutic proteins (eg, monoclonal antibodies).
11. Has experienced myocardial infarction, unstable ischemic heart disease, or stroke
within 12 weeks of screening.
12. A post-pubertal male participant is planning to father a child while enrolled in this
study or donate sperm within 90 days after the last administration of study intervention.
13.
13.1 A female of childbearing potential is currently breastfeeding, pregnant, intends to
become pregnant during the study, or is planning egg donation during the study or
within 30 days after the last dose of study intervention.
14. History of moderate or severe substance or alcohol use disorder according to Diagnostic
and Statistical Manual of Mental Disorders (5th edition) (DSM-5) criteria, except
nicotine or caffeine, within 1 year before Screening.
Prior/Concomitant Therapy
15. Is currently taking eculizumab or other novel immune agents, IgG Fc-related protein therapeutics, or Fc-conjugated therapeutic agents, including factor or enzyme
replacement.
16. Has received, rituximab within 6 months prior to first administration of study
intervention.
17. Has received or is expected to receive a live vaccine within 4 weeks prior to
screening or has a known need to receive a live vaccine during the study, or within
8 weeks after the last administration of study intervention. For the Bacille CalmetteGuerin
(BCG) vaccine, see exclusion criterion 33. Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for
severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), unless it is a live
vaccine. Concomitant enrollment in an investigational trial for any SARS-CoV-2 (COVID-19) vaccine while participating in this study is not permitted.
18. Has received plasmapheresis, immunoadsorption therapy, or IVIg within 4 weeks prior

to baseline.
19. Has another medical condition that requires oral or parenteral corticosteroids unless the dose has been stable for at least 4 weeks prior to baseline and is expected to remain stable during the study. Inhaled, intra-articular, topical or ocular corticosteroids are not exclusionary.
20. Has another medical condition that requires an immunosuppressive agent unless the medication has been used for at least 6 months, the dose has been stable for at least 3 months prior to baseline and the medication and the dose are expected to remain stable during the study.
21. Has previously received nipocalimab.
22. Has received an investigational intervention (including investigational vaccines) within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months before the planned first dose administration of study intervention [or is currently enrolled in an investigational study]. Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for SARS-CoV-2.
23. Has a severe infection including opportunistic infections (eg, pneumonia, biliary tract infection, diverticulitis, Clostridium difficile infection, cytomegalovirus, pneumocystosis, aspergillosis, etc.) requiring parenteral anti-infectives and/or hospitalization, and/or is assessed as serious/clinically significant by the Investigator, within 8 weeks prior to Screening. The participant may be re-screened after the 8-week exclusionary period has passed.
24. Has a chronic infection (eg, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (eg, antibiotics, antivirals).
25. Tests positive for hepatitis B virus (HBV) infection (see Section 10.3, Appendix 3: Hepatitis B Virus (HBV) Screening with HBV DNA).
26. Is seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy 1 of the following conditions:

Has a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,
OR
While seropositive, has a negative HCV RNA test result at least 24 weeks prior to screening and a negative HCV RNA test at screening.
27. History of human immunodeficiency virus (HIV)1 or HIV2 antibody-positive, or tests positive for HIV at screening.
28. COVID-19 infection:
During the 6 weeks prior to baseline, 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 SARS
CoV-2 test
* obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key c

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-11-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nipocalimab
Generic name:	nipocalimab

Ethics review

Approved WMO Date:	28-04-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-09-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	21-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EU-CTR	CTIS2022-502539-21-00
EudraCT	EUCTR2021-002479-20-NL
ClinicalTrials.gov	NCT05265273
CCMO	NL79880.058.22