Efficacy and Safety of M281 in Adults with Warm Autoimmune Hemolytic Anemia: A Multicenter, Randomized, Double blind, Placebo controlled Study with a Long-term Open-label Extension

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This study has been transitioned to CTIS with ID 2023-505321-14-00 check the CTIS register for the current data. Primary Objective:Efficacy of nipocalimab in participants with warm autoimmune hemolytic anemia (wAIHA)The key secondary objectives of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haemolyses and related conditions
Study type	Interventional

Summary

ID

NL-OMON54686

Source
ToetsingOnline

Brief title
MOM-M281-006

Condition

- Haemolyses and related conditions
- Autoimmune disorders

Synonym
wAIHA, Warm Autoimmune Hemolytic Anemia

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag International NV
Source(s) of monetary or material Support: Momenta Pharmaceuticals;Inc.

Intervention

Keyword: M281, Warm Autoimmune Hemolytic Anemia

Outcome measures

Primary outcome

Durable response in improvement in hemoglobin (Hgb), defined as attainment of the following at 3 consecutive visits (minimum duration 28 days) , where at least the first is at or before Week 16, without the need of rescue therapy:

• Hgb concentration >=10 g/dL AND

• An increase from baseline in Hgb >=2 g/dL

Secondary outcome

Key secondary endpoints:

-Change in the level of participant fatigue. Change from baseline in the total score from the FACIT-Fatigue Scale at the time of durable response.

-Change from baseline in the total score from the FACIT-Fatigue Scale at the end of the double-blind period (Week 24)

-Percent reduction from baseline in average daily dose of prednisone or equivalent at Week 24 of the double-blind period among participants on prednisone or equivalent at baseline.

Other Secondary Endpoints:

-Normalization of hemolytic markers

1. Proportion of participants who simultaneously attain normal lactate

dehydrogenase (LDH), AND normal haptoglobin, AND normal indirect bilirubin levels at 3 consecutive visits.

2. Attainment of a 2 g / dl Hgb increase from baseline AND normal LDH, and haptoglobin, and indirect bilirubin levels at any time during the study

3. Attainment of a 2 g / dl Hgb increase from baseline AND normal LDH and, haptoglobin, and indirect bilirubin levels at 3 consecutive visits

Normalization of hematologic and hemolytic parameters:

-Hgb concentration, reticulocyte count, and hemolytic markers, and change from baseline in these parameters through Week 16 of the double-blind period

-Hgb, reticulocyte count, and hemolytic markers, and change from baseline in these parameters through the study

Effect of nipocalimab on maintaining response in Hgb

-Proportion of participants wo achive the durable response in improvement of Hgb and maintain that response for up to 24 weeks throughout the study without the need of rescue therapy.

-Time to and duration of Hgb response

1. Time to response defined as the first time point at which the durable response criteria for the primary efficacy endpoint is met

2. Duration from the first time point at which the durable Hgb response criteria for the primary efficacy endpoint is met until the time point at which it is no longer met

-Change in the level of participant fatigue:

Change from baseline in the total score, item scores and impact and experience domains from the FACIT-Fatigue Scale through Week 24 of the double-blind period

-Changes in health-related quality of life parameters based on EQ-5D-5L, SF-36, PGIS, PGIC

-Impact of nipocalimab on corticosterioid use

Absolute reduction from baseline in average daily dose of prednisone or equivalent at Week 24 of the double-blind period amont all participants

The proportion of participants who achieve corticosterioid reduction to <= 7.5 mg/day of oral prednisone (or equivalent) at Week 24 of double-blind period among participants on prednisone or equivalent >7.5 mg/day at baseline

The proportion of participants who achieve the durable response in improvement of Hgb during the double-blind period and maintain that response for upt to 24 weeks throughout the study without the need of rescue therapy will be summarized descriptively.

Study description

Background summary

Autoimmune hemolytic anemia (AIHA) is a rare, life-threatening autoimmune disorder. Warm AIHA is the most common form of AIHA. Conventional treatment of wAIHA usually includes corticosteroids as first-line therapy; however, this treatment produces long-term remission in only ~30% of patients and is associated with side effects that limit their use.
In wAIHA cases involving relapse or refractory disease, splenectomy may be used as second line therapy since the spleen is the major organ for antibody synthesis and immune destruction of IgG-coated RBCs. However, splenectomy is ineffective in about 35 to 40% of cases and is also associated with serious risks including overwhelming post-splenectomy infection, with an estimated lifetime risk of 0.1 to 0.5% and a mortality rate of up to 50%. Other immunosuppressive drugs such as azathioprine, cyclophosphamide, ciclosporin, danazol, and rituximab are also used as second-line therapies, with response rates of 40 to 60%, but these therapies also have severe side effects.

The sponsor is developing M281 for the treatment of wAIHA, with an initial focus on patients with active, primary or secondary wAIHA. M281 is a fully human, aglycosylated IgG antibody that targets the IgG binding site on the neonatal FC receptor (FcRn). FcRn is a transmembrane protein expressed by endothelial cells (especially vascular endothelial cells), cells of the immune system (including monocytes, macrophages, dendritic cells, and neutrophils), and most epithelial cells, including syncytiotrophoblasts in the placenta. The primary role of FcRn in humans is to bind, salvage, and recycle IgG into the circulation following nonspecific pinocytosis into the reticuloendothelial system. Administration of M281 to wAIHA patients is expected to rapidly ameliorate the physical and laboratory manifestations of the disease by blocking FcRn-mediated recycling of IgG and reducing circulating levels of antibodies, including the pathogenic autoantibodies that cause wAIHA. Based on its mechanism of action, M281 is expected to increase catabolism and thus reduce exposure of therapeutic agents that incorporate the Fc region of IgG. This includes intravenous immunoglobulin (IVIg) and most therapeutic monoclonal antibodies and Fc fusion proteins.

Study objective

This study has been transitioned to CTIS with ID 2023-505321-14-00 check the CTIS register for the current data.

Primary Objective:
Efficacy of nipocalimab in participants with warm autoimmune hemolytic anemia (wAIHA)

The key secondary objectives of this study are to evaluate the::
Impact of nipocalimab treatment on fatigue
Impact of nipocalimab on corticosteroid use

Other secondary objectives of this study are to evaluate the:
effects of nipocalimab on normalization of hemolytic markers
effects of nipocalimab on maintaining response in Hgb
effects of nipocalimab on normalization of hematologic and hemolytic parameters
effects of nipocalimab on the time to, and the duration of, Hgb response
impact of nipocalimab treatment on fatique improvement
effects of nipocalimab on health-related quality of life and health status
association between IgG reduction and Hgb/hemolysis parameters
impact of nipocalimab on the reduction of corticosteroid dose

Study design

Randomized, double-blind, placebo-controlled study

Intervention

In the double-blind period, approximately 111 eligible participants will be enrolled and randomized 1:1:1 to 1 of 3 treatment groups:
• Group 1 (n=37): Placebo intravenous (IV) infusion every 2 weeks (Q2W)
• Group 2 (n=37): 30 mg/kg nipocalimab IV infusion every 4 weeks (Q4W)
• Group 3 (n=37): 15 mg/kg nipocalimab IV infusion Q2W

Study burden and risks

Nipocalimab is a drug that lowers the level of a group of proteins in the blood called IgG (immunoglobulin G). IgG is a kind of antibody, and antibodies help fight infections. There may be increased risk of infection while you are receiving nipocalimab and for a few weeks after the last dose of nipocalimab. You will be monitored for signs of infections during your participation in the study. Tell your investigator if you experience any new symptoms or a worsening of your previous symptoms. have a new infection, if an infection keeps coming back, or if you have any signs of infection, such as:
• fever
• chills
• headache
• coughing
• congestion
• chest tightness
• shortness of breath
• flu-like symptoms
• nausea
• vomiting
• diarrhea
• increased frequency or burning while passing urine
• redness warmth, tenderness or swelling of skin or joint
• cold sores
• new or worsening of pain in any location
• weight loss
• tiredness
• night sweats
• vaginal itching or discharge
• white patches in the mouth or on the tongue

Contacts

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Janssen-Cilag International NV

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Scientific
Janssen-Cilag International NV

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BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria, Double-blind Period
Patients who meet the following criteria will be eligible for enrollment into the double-blind period of the study.
1. Male or female >=18 years of age.
2. Diagnosed with active primary or secondary wAIHA, defined as having all of the following:
a) Hgb value<10 g / dl AND
b) Signs of hemolysis, defined as: lactate dehydrogenase (LDH) levels above the upper limit of normal (ULN), or haptoglobin below the lower limit of normal, or indirect bilirubin above the ULN AND
c) Serological evidence of anti erythrocyte antibodies associated with a DAT that is either positive for IgG only or is positive for IgG and C3d (fragment of the third component of complement) at screening at the central laboratory. If the DAT is negative, it can be repeated once. If the repeat is negative, participant not eligible.
3. Have been diagnosed with wAIHA for at least 3 months, and are currently receiving treatment for wAIHA OR have previously received treatment for wAIHA (treatment-naïve participants are not eligible)
4. If on corticosteroids, participants must have been on treatment for at least

4 weeks with a stable dose during the screening period or for at least 14 days prior to randomization. whichever is longer. Note:
Investigators can optimize the above background medications prior to randomization if they are following the above rules for stable dose duration.
5. If receiving immunosuppressants, following drugs allowed:
concomitant immunosuppressants are azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate,
cyclosporine, tacrolimus, danazol, and cyclophosphamide. Participants must have been on a stable dose of any of
these drugs for =12 weeks prior to screening and during the screening period.
If any of these drugs were stopped,
it must have been stopped for at least 8 weeks prior to screening. Note:
Investigators can optimize the above background medications prior to randomization if they are following the above rules for stable dose duration.
6. Have a platelet count >=30 × 109/L.
Note: Patients with Evans syndrome who do not have primary immunodeficiency will be eligible as long as they meet all other entry criteria, including having a platelet count >=30 × 109/L.
7. Participants who have undergone 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 (CDC) annual Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States (https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html) OR must be vaccinated as per country-specific guidelines (Davies 2011).
8. Participants with other autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis) or lymphoproliferative disorders may be eligible if they are stable (no changes in concomitant disease-related medications and severity of disease) for at least 3 months prior to screening. Participants with lymphoproliferative disease must also have a low grade, be stable and be, in the opinion of the Investigator, unlikely to require chemotherapy or monoclonal antibody therapy during the double-blind period of the study. Participants requiring change of treatment or new treatment for autoimmune or lymphoproliferative diseases ((but not rescue therapy for wAIHA) during the double-blind period will be terminated from the study.
9. Have sufficient venous access to allow drug administration by IV infusion and blood sampling as per the protocol.
10. Women of childbearing potential, defined as women physiologically capable of becoming pregnant, must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Menopausal women must have an elevated serum follicle-stimulating hormone (FSH) level at screening; if the FSH is not elevated, they are considered to be of childbearing potential and must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline to be eligible.
11. Women of childbearing potential (including menopausal women who do not have elevated FSH) must agree to remain totally abstinent or to consistently use a reliable and highly effective method of contraception during the study and for 30 days after the last dose of study drug.

12. 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 dose of study drug. In addition, male participants with partners who are a woman of childbearing potential are to be highly encouraged to inform their partner to use highly effective contraception methods that result in low failure rate (less than 1% per year)
13. Participants who use herbal, naturopathic, traditional Chinese remedies, ayurvedic and nutritional supplements, or medical marijuana (with a doctor*s prescription) are eligible if the use of these medications is acceptable to the Investigator. These remedies must be at a stable dose and regimen using the same preparation for >=2 months prior to Screening.
14. Are able to understand and voluntarily provide written informed consent to participate in the study and comply with all study procedures. Patients who initially provide consent and subsequently withdraw it prior to randomization, will be deemed as having failed this inclusion criterion.
15. Vaccinations prior to screening as per routine local guidelines (including COVID-19).

Inclusion Criteria, Open-label Extension
1. Participants have completed the double-blind period (through Week 24), or have required rescue therapy at/or after Week 4 of the double-blind period, or failed to demonstrate an increase from baseline in Hgb of at least 1 g/dL and are symptomatic at or after Week 16 of the double-blind period.
2. Are able to understand and voluntarily provide written informed consent to participate in the OLE period and comply with all study procedures.

Exclusion criteria

Exclusion Criteria, Double-blind Period
Patients who meet any of the following criteria will not be eligible for enrollment into the double-blind period of the study.
1. Are currently taking IgG Fc-related protein therapeutics.
2. Have received a transfusion within 30 days prior to randomization.
3. Have any other associated cause of hereditary or acquired hemolytic anemia.
4. Have received rituximab within 3 months prior to screening.
5. Have received IVIg within 6 weeks prior to screening.
6. Have been diagnosed with cold antibody AIHA, cold agglutinin syndrome, mixed type (i.e., warm and cold) AIHA, or paroxysmal cold hemoglobinuria.
7. Have a severe infection (e.g., pneumonia, biliary tract infection, diverticulitis, Clostridium difficile infection) that requires parenteral anti-infectives and/or hospitalization, and/or is assessed as serious/clinically significant (CS) by the Investigator, within 8 weeks prior to screening. Any participant with an infection requiring oral anti-infectives (e.g., sinusitis, bronchitis, uncomplicated urinary tract infection) within 4 weeks prior to screening will be excluded.

8. Have a chronic infection (e.g., bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or require chronic treatment with anti-infectives (e.g., antibiotics, antivirals).
9. Have received a live viral or bacterial vaccine within 4 weeks prior to first dose of study drug, or have a known need to receive a live viral or bacterial vaccine during the study or within at least 3 months after the last dose of study drug. For information regarding the Bacille Calmette-Guérin (BCG) vaccine, please see Exclusion Criterion 25.
10. Have any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of their wAIHA, or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the participant.
11. Have any of the following viral testing outcomes:
• A history of human immunodeficiency virus (HIV) infection or positive test result for HIV-1 and HIV 2 antibodies.
• A positive test for hepatitis B virus surface antigen (HBsAg). For participants with a negative test for HBsAg along with a positive test for anti-hepatitis B core (HBc) antibodies and a positive or negative test for anti-HBs antibodies, hepatitis B viral DNA detection will be performed. Participants with a positive hepatitis B viral DNA detection will be excluded. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol; A positive test for hepatitis C virus (HCV) unless 1 of the following conditions are met: (a) 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 least 24 weeks prior to screening and a negative HCV RNA test at the screening.
12. Are currently breastfeeding, pregnant, intend to become pregnant during the study, or are planning egg donation during the study or within 30 days after the last dose of study drug.
13. Have current alcohol/substance abuse/dependence, a history of alcohol/substance abuse/dependence within the 12 months prior to screening, or, in the Investigator*s opinion, show evidence of ongoing alcohol/substance abuse/dependence.
14. Are currently participating in another interventional clinical trial or have received any investigational drug within the past 3 months prior to screening.
15. Have had any major surgery within 3 months prior to screening or have plans for or have been scheduled for any elective surgery or major dental procedure during the study.
16. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver), or hematopoietic stem cell/marrow transplant.

Further exclusion criteria listed in the protocol not listed here due to character restriction.

Exclusion Criteria, Open-label Extension
1. Met any of the stopping criteria (see Section 6.4.1) or discontinued study

drug during the double-blind period due to treatment-related AE.
2. Currently have a serious or clinically significant infection (e.g., pneumonia, biliary tract infection, diverticulitis, C. difficile infection) requiring parenteral anti-infectives and/or hospitalization.

The following exclusion criterion from the double-blind period also applies to enrollment in the OLE: Exclusion Criteria #8 and #21.
Exception: Participants who were previously enrolled in this study and was unable to complete the DBP due to the Sponsor suspending dosing due to the COVID-19 pandemic can be enrolled in the OLE after meeting all of the double-blind eligibility criteria. Participants who completed the 28-week OLE before Amendment 6 can be re-enrolled in the OLE per investigator's discretion if the participants continue meet the eligibility criteria for the OLE.
Participants will resume study treatment calculated from the baseline visit once they have reconsented to the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2023
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	16-09-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-10-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-11-2021
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-09-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	CTIS2023-505321-14-00
EudraCT	EUCTR2019-000720-17-NL
CCMO	NL70399.100.19