A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

Published: 27-11-2018
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Primary:• To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH Secondary• To characterize PK of ravulizumab SC• To characterize PD of ravulizumab SC• To characterize immunogenicity of ravulizumab SC• To...

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

Summary

ID

NL-OMON52568

Source
ToetsingOnline

Brief title
ALXN1210-PNH-303

Condition

- Red blood cell disorders

Synonym
Paroxysmal Nocturnal Hemoglobinuria; red blood cell disorder

Research involving
Human

Sponsors and support

Primary sponsor: Alexion Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Alexion Pharmaceuticals;Inc

Intervention

Keyword: Intravenously, Paroxysmal Nocturnal Hemoglobinuria (PNH), Ravulizumab, Subcutaneously

Outcome measures

Primary outcome

Primary PK endpoint: Day 71 serum ravulizumab C-trough

Secondary outcome

PK Endpoint: C-trough over time

PD Endpoint: Free serum C5 concentrations over time

Immunogenicity Endpoint: Incidence of treatment-emergent ADAs over time

HRQoL and Treatment Satisfaction Endpoints:

• Change in FACIT-Fatigue Scale, Version 4, from Baseline to Day 183

• Change in EORTC QLQ-C30 Version 3.0, from Baseline to Day 183

• Reported treatment satisfaction and patient preference as measured by the

TASQ score at Baseline and Day 183

Safety Endpoints:

• Change in physical examinations, vital signs, electrocardiograms, and

laboratory assessments over time

• Incidence of adverse events and serious adverse events

• Incidence of adverse device effects and serious adverse device effects

Efficacy Endpoints:

• Change over time in LDH

• Incidence of breakthrough hemolysis

• Achievement of transfusion avoidance

• Achievement of stabilized hemoglobin

Performance Endpoint:

• Reported outcome of attempted full-dose administration (including device

failure/malfunction)

Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra rare and life threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway. Chronic, uncontrolled complement component 5 (C5) cleavage and release of C5a and C5b 9 lead to red blood cell (RBC) hemolysis. Hemolysis results in the release of intracellular free hemoglobin and lactate dehydrogenase (LDH) into circulation; irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin and inhibition of NO synthesis; vasoconstriction and tissue bed ischemia due to absence of vasodilatory NO as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; platelet activation; and a proinflammatory and prothrombotic state. A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension. Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system. Secondary effects in addition to the risk of major end organ

damage from thrombosis include abdominal pain, extreme or unrelenting fatigue, difficulties in concentrating or thinking, and reduced activities of daily living (ADL).
The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block intravascular hemolysis and thereby prevent thrombosis.
Currently, the only approved treatment for PNH that blocks terminal complement activity is eculizumab (Soliris®), a humanized monoclonal antibody (mAb) derived from the murine anti-human C5 antibody m5G1.1 and specifically binds to the complement protein C5 with high affinity. Eculizumab is administered by intravenous (IV) infusion every other week.
Ravulizumab (ALXN1210) is a humanized mAb that binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b. Ravulizumab was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain (Sheridan, 2018). These changes extend the half life of ravulizumab relative to eculizumab, while preserving the high degree of specificity and selectivity for binding to C5 of eculizumab.
The purpose of this study is to compare the Pharmacokinetic (PK), specifically predose serum concentration (Ctrough), of ravulizumab SC administered via an OBDS versus ravulizumab IV administration in patients who are clinically stable and have been treated with eculizumab for at least 6 months prior to study entry.
The efficacy of ravulizumab IV was shown to be noninferior to eculizumab in Phase 3 clinical studies in complement inhibitor-naïve patients and in patients who had previously received treatment with eculizumab. Ravulizumab SC may provide additional benefit by reducing the treatment burden associated with chronic IV dosing. The safety of ravulizumab SC via an OBDS in patients with PNH at the doses specified in this protocol is supported by data from clinical studies of ravulizumab IV and SC in healthy volunteers and clinical studies of ravulizumab IV in patients with PNH, in addition to postmarketing data on the West Smart Dose Platform used with other approved therapies. The benefit/risk of ravulizumab SC administration to patients with PNH is anticipated to be favorable.

Study objective

Primary:
• To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH

Secondary
• To characterize PK of ravulizumab SC
• To characterize PD of ravulizumab SC
• To characterize immunogenicity of ravulizumab SC

• To evaluate HRQoL and treatment satisfaction on ravulizumab SC
• To evaluate safety of ravulizumab SC and ravulizumab OBDS
• To evaluate efficacy of ravulizumab SC
• To assess performance of ravulizumab OBDS

Study design

This is a Phase 3, randomized, open-label, parallel-group, multicenter study to evaluate PK noninferiority of ravulizumab SC administered via an OBDS compared with intravenously administered ravulizumab IV in adult patients with PNH who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry.

The study will consist of an up to 30-day Screening Period, a 10-week Randomized Treatment Period, and an Extension Period of up to 3.5 years (182 weeks) or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first. Patients will be stratified by weight group (>= 40 kg to < 60 kg and >= 60 kg to < 100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

Intervention

Ravulizumab subcutaneously (SC):
- Loading Dose on Day 1: Ravulizumab IV 2400 mg (Weight group >= 40 to < 60 kg) or Ravulizumab IV 2700 mg (Weight group >= 60 to < 100 kg)
- SC Doses on Days 15, 22, 29, 36, 43, 50, 57, and 64:Ravulizumab SC 490 mg (2 ravulizumab OBDS kits per weekly dose; On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for self-administration at home. On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab SC can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits.)
- Maintenance Doses on Day 71 and qw through Day 1275: Ravulizumab SC 490 mg (2 ravulizumab OBDS kits per weekly dose; Self-administered by the patient)

Ravulizumab intravenously (IV):
- Loading Dose on Day 1: Ravulizumab IV 2400 mg (Weight group >= 40 to < 60 kg) or Ravulizumab IV 2700 mg 9 Weight group >= 60 to < 100 kg)
- Maintenance Dose on Day 15: Ravulizumab IV 3000 mg (Weight group >= 40 to < 60 kg) or Ravulizumab IV 3300 mg ((Weight group >= 60 to < 100 kg)
- Maintenance Doses on Day 71 and qw through Day 1275: Ravulizumab SC 490 mg (2 ravulizumab OBDS kits per weekly dose; Self-administered by the patient at home

or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.)

Study burden and risks

Patients are asked to undergo procedures described on pages 18-28 of the study protocol. The study will consist of an up to 4-week Screening Period, a 10-week Randomized Treatment Period, and a 182-week Extension Period. The study procedures include physical examination, blood and urine sample collection, vital signs, ECG, meningococcal vaccination (if not done before), completion of questionnaires and eDiary, answer questions of investigator and study team and administration of study drug including using an OBDS device for subcutaneous administration.
Additionally, fertile subjects are asked to use contraceptives, and female subjects of childbearing potential will have pregnancy tests and blood will be taken for HIV testing.

The study medication as well performing the study-related procedures may cause discomforts and risks. Ravulizumab may also have discomforts and risks that are still unknown. These may be mild or serious, and in some cases may be very serious, long-lasting, or may never go away. There is also a risk of death.
Following side effects have been reported based on the clinical experience in patients with PNH using Ravulizumab.
Meningococcal Infection: Patients receiving ravulizumab, even after a single dose, are at increased risk for development of serious infections caused by Neisseria meningitidis. This is a bacterial infection that can the brain (meningococcal meningitis) or be present in blood (meningococcal sepsis). Meningococcal infections can rapidly become life-threatening or fatal especially if not recognized and treated early. Subjects will receive a vaccination against meningococcal infections. Vaccination alone may not be sufficient to prevent infection with Neisseria meningitidis.
Very common side effects (seen in more than 10 % of PNH patients): upper respiratory tract infection, nasopharyngitis, headache
Common side effects (seen in 1% to 10% of PNH patients): nausea, abdominal pain, vomiting, diarrhea, indigestion, flu-like illness, fever, tiredness, muscle pain and spasms, back pain, joint pain, dizziness, rash and itchiness
Uncommon side effects (seen in less than 1% of PNH patients): meningococcal infection and meningococcal sepsis (blood infection), chills
Study Procedures:
Blood draws - Subjects may experience pain, bruising, or bleeding at the site of puncture. There is also the possibility of infection. Although the total amount of blood drawn over time is predicted to be well tolerated, anemia may

occur.

Intravenous (IV) infusions - There may be discomfort during IV placement, on rare occasions this may cause pain, bleeding, bruising, swelling, clotting of the vein, leakage of medication or solution into the surrounding tissues, and possibly infection at the insertion site of the IV line.

Subcutaneous (SC) infusions - Study drug is administered with an injection under the skin using 2 OBDS devices per dose. Subjects may experience localized pain, redness, itchiness, bruising, rash, or infection at the site where the SC injection is given.

On-body delivery system (OBDS) device - This is a wearable, single use patch injector. It is intended to be worn on the body (upper arm, abdomen, or thigh) for about 10 minutes. It is attached to the body with an adhesive (like a band-aid) and removed when the SC infusion is completed. As with any adhesive, there may be a small risk of skin irritation. Some symptoms of skin irritation at the site may include: rash, itchiness, and redness.
The meningococcal vaccination can cause temporary local swelling at the injection site.

The efficacy of ravulizumab IV was shown to be noninferior to eculizumab in Phase 3 clinical studies in complement inhibitor-naïve patients and in patients who had previously received treatment with eculizumab. Ravulizumab SC may provide additional benefit by reducing the treatment burden associated with chronic IV dosing. The safety of ravulizumab SC via an OBDS in patients with PNH at the doses specified in this protocol is supported by data from clinical studies of ravulizumab IV and SC in healthy volunteers and clinical studies of ravulizumab IV in patients with PNH, in addition to postmarketing data on the West Smart Dose Platform used with other approved therapies. The benefit/risk of ravulizumab SC administration to patients with PNH is anticipated to be favorable.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Patients must be at least 18 years of age at the time of signing the informed consent.
2. Treated with eculizumab according to the labeled dosing recommendation for PNH (900 mg every 14 days ± 2 days) for at least 3 months prior to study entry with no missed doses within 2 months prior to study entry and no more than 2 doses outside of the visit window.
3. Lactate dehydrogenase levels <= 1.5 × ULN (upper limit of normal), according to central laboratory, at Screening. Sample must be obtained within 24 hours of or immediately prior to a scheduled eculizumab dose administration (ie, at trough eculizumab level).
4. Documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010).
5. Vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug to reduce the risk of meningococcal infection (N meningitidis).
6. Body weight > 40 to < 100 kg, and in the opinion of the Investigator, are likely to remain within this body weight range for the duration of the study.
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified contraception guidance while on treatment and for at least 8 months after last dose of study drug.
8. Patients (or their legally authorized representative) must be willing and able to give written informed consent and to comply with all study visits and procedures, including self administration of ravulizumab SC doses, and the use

of any data collection device(s) to directly record patient data.

Exclusion criteria

1. More than 1 LDH value > 2 × ULN within the 3 months prior to study entry.
2. Major adverse vascular event (MAVE) in the 6 months prior to study entry.
3. Platelet count < 30,000/mm3 (30 × 10*9/L) at Screening.
4. Absolute neutrophil count < 500/µL (0.5 × 10*9/L) at Screening.
5. History of bone marrow transplantation.
6. History of N meningitidis infection.
7. History of unexplained infections.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
9. Presence of fever >= 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
10. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
11. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
12. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient*s participation in an investigational clinical study.
13. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Day 1, coexisting chronic anemia unrelated to PNH) that would make patients unlikely to tolerate the requirements of the protocol).
14. History of hypersensitivity to any ingredient contained in the study drug including hypersensitivity to murine proteins.
15. Female patients who plan to become pregnant or are currently pregnant or breastfeeding.
16. Female patients who have a positive pregnancy test result at screening or on Day 1.
17. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient*s full participation in the study, pose an additional risk for the patient, or confound the outcome of the study.
18. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to Screening.
19. Inability to complete the requirements for SC self-administration.
20. Inability to travel to the clinic for specified visits during the Randomized Treatment Period or fulfil the logistic requirements of study drug.
21. Concomitant use of anticoagulants is prohibited if not on a stable regimen

for at least 2 weeks prior to study entry.
22. Participation in another study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater (except for participation in observational studies [eg, PNH Registry]).
23. Received any other experimental C5 antagonist at any time.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Generic name:	Ravulizumab on-body delivery system (OBDS)
Registration:	No
Product type:	Medicine
Brand name:	Ravulizumab
Generic name:	Ravulizumab

Ethics review

Approved WMO Date:	27-11-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-07-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-07-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	28-07-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-05-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-08-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	128367
EudraCT	EUCTR2017-002370-39-NL
CCMO	NL67982.068.18