A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON45425

Source
ToetsingOnline

Brief title
PNH-301

Condition

- Red blood cell disorders

Synonym
bleeding disorder

Research involving

Human

Sponsors and support

Primary sponsor: Alexion Pharmaceuticals
Source(s) of monetary or material Support: pharmaceutical company

Intervention

Keyword: ALXN1210, complement inhibitor treatment, lactate dehydrogenase normalization, PNH

Outcome measures

Primary outcome

The coprimary efficacy endpoints of the study are:

* Transfusion avoidance, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26)

* Hemolysis as directly measured by LDH-N levels from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)

Secondary outcome

1. Percentage change in LDH from Baseline to Day 183 (Week 26)

2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183 (Week 26)

3. Proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE, including

thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated

LDH * 2 × upper limit of normal [ULN], after prior LDH reduction to < 1.5 × ULN

on therapy

4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a

* 2 g/dL decrease in hemoglobin level from baseline in the absence of

transfusion through Day 183 (Week 26)

Pharmacokinetic and Pharmacodynamic Endpoints

* Change in serum ALXN1210 and eculizumab concentration over time

* Change in chicken red blood cell (cRBC) hemolytic activity over time

(exploratory)

* Change in free complement component 5 (C5) concentrations over time

More details for end points can be found in protocol section 6.2.

Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder that occurs most frequently in adults. The pathology and clinical presentations in patients with PNH are driven by uncontrolled terminal complement activation on red blood cells (RBCs).
The only approved treatment for PNH is eculizumab (Soliris®). Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein C5 with high affinity. ALXN1210 was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (1 month or longer). ALXN1210 and eculizumab share > 99% amino-acid sequence homology.
The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement

activity to block hemolysis and prevent thrombosis. More specifically, incomplete C5 blockade may increase risk of potentially life-threatening breakthrough hemolysis (Hill 2012a, Lee 2013). Any loss of efficacy at the end of a dosing interval or missed doses due to inconvenience of dosing intervals may put patients at substantial medical risk. Patients treated with eculizumab are required to receive maintenance infusions every 2 weeks. Given that PNH is a chronic disease, this regimen may have a significant impact on patients in terms of individual patient concerns associated with missed work and more importantly may impact treatment compliance.
ALXN1210 has been designed to have the same rapid onset of action and effective blockade of complement, with an increased serum half-life to yield an increased duration of pharmacologic activity relative to eculizumab. The substantially longer half-life of ALXN1210 is expected to produce sustained terminal complement inhibition during a longer dosing interval and thus reduce the potential risk of breakthrough complement-mediated hemolysis during the treatment period, thus improving the overall health of patients.

Study objective

The primary objective of this study is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who have never been treated with a complement inhibitor.
Noninferiority will be claimed if after 26 weeks of treatment: 1) the lower bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in transfusion avoidance (TA) rate is greater than -20%, and 2) the lower bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab for lactate dehydrogenase normalization (LDH-N) is greater than 0.39.

Secondary Objectives
The secondary objectives of the study are to assess the following:
* To characterize the safety and tolerability of ALXN1210 in this patient population
* To evaluate the efficacy of ALXN1210 by additional efficacy measures
* To characterize the pharmacokinetics/pharmacodynamics (PK/PD) and immunogenicity of ALXN1210
* To evaluate the long-term safety and efficacy of ALXN1210
* To evaluate the safety and efficacy in patients who switch from eculizumab to ALXN1210 in the Extension Period

Study design

Study ALXN1210-PNH-301 is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who are naïve to complement inhibitor treatment. The study will enroll approximately 214 patients (107 patients per treatment group).

The study consists of a 4-week screening period, a 26 week randomized treatment period, and an extension period of up to 2 years. Patients will be stratified into 1 of 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × ULN or * 3 × ULN). The patients within each of the 6 groups will then be randomly assigned in a 1:1 ratio to receive ALXN1210 or eculizumab. Enrollment of patients without a history of transfusion in the past year will be capped at 20%.

Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient*s hemoglobin must be evaluated by either local or central laboratory. If at that time the patient*s hemoglobin value meets protocol-specified transfusion guidelines, the patient must be transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient*s post-transfusion hemoglobin value should be confirmed by local or central laboratory to be above the protocol-specified transfusion threshold.

Patients randomly assigned to the ALXN1210 group will receive a loading dose of ALXN1210 (2400 mg for patients weighing * 40 to < 60 kg, 2700 mg for patients weighing * 60 to < 100 kg, 3000 mg for patients weighing * 100 kg) on Day 1, followed by maintenance doses of ALXN1210 (3000 mg for patients weighing * 40 to < 60 kg, 3300 mg for patients weighing * 60 to < 100 kg, 3600 mg for patients weighing * 100 kg) on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group will receive induction treatment with 600 mg of eculizumab IV on Days 1, 8, 15, and 22, followed by maintenance treatment with eculizumab 900 mg on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. After completion of all assessments on Day 183, patients will enter an extension period and receive ALXN1210 until the product is registered or approved (in accordance with country-specific regulations) or for up to 2 years, whichever occurs first. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive a maintenance dose (as described above) of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose (as described above) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210.

Intervention

Administration of study studydrug ALXN1210 and eculizumab (active control) via IV infusion. Dosage is based on patients weight.

Study burden and risks

Potential risks associated with ALXN1210 include infections (N. meningitidis

and other encapsulated organisms), immunogenicity, and hypersensitivity.
Please refer to the IB, section 2.2 for a detailed description of Potential Risks Associated with ALXN1210, Summary of Data, and Monitoring Guidance for the Investigator

Contacts

Public
Alexion Pharmaceuticals

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US
Scientific
Alexion Pharmaceuticals

College Street 100
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female * 18 years of age
2. PNH diagnosis confirmed documented by high-sensitivity flow cytometry
3. Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.

4. LDH level * 1.5 × ULN at screening.
5. Documented meningococcal vaccination not more than 3 years prior to, or at the time of, initiating study treatment.
6. Female patients of childbearing potential must use highly effective contraception starting at screening and continuing until at least 8 months after the last dose of ALXN1210
7. Willing and able to give written informed consent and comply with study visit schedule

Exclusion criteria

1. Treatment with a complement inhibitor at any time.
2. History of bone marrow transplantation.
3. Body weight < 40 kilograms.
4. Females who are pregnant, breastfeeding or who have a positive pregnancy test at screening or Day 1
5. Participation in another interventional clinical 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.
6. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease that, in the opinion of the investigator or sponsor, would preclude participation
7. Unstable medische conditions (bv, myocardial ischemia, actieve gastrointestinal bloedingen, zware congestive hartfalen, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH).

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: Will not start

Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ALXN1210
Generic name:	-
Product type:	Medicine
Brand name:	Soliris
Generic name:	Eculizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-11-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-03-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	19-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-002025-11-NL
ClinicalTrials.gov	NCT02946463
CCMO	NL58963.091.16