A PHASE 3, OPEN-LABEL STUDY OF ALXN1210 IN CHILDREN AND ADOLESCENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

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The primary objective of this study is to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, andefficacy of ALXN1210 in pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH).

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

Summary

ID

NL-OMON50200

Source
ToetsingOnline

Brief title
ALXN1210-PNH-304

Condition

- Haemolyses and related conditions

Synonym
blood disorder, PNH

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALXN1210, Children en adolescents, Open label, phase 3

Outcome measures

Primary outcome

Primary endpoint:

* PK/PD parameters (trough and peak) at Baseline and Weeks 2, 10, 18, and 26

o PK: maximum serum concentration (Cmax), trough serum concentration (measured

at end of dosing

interval at steady state; Ctrough), accumulation ratio

o PD: change in free C5 concentrations and in chicken red blood cell (cRBC)

hemolytic activity over time

Secondary outcome

Secondary endpoint:

* Percentage change in LDH from baseline to Day 183 (Week 26)

* Transfusion avoidance (TA), defined as the proportion of patients who remain

transfusion-free and do not

require a transfusion through Day 183 (Week 26)

* Change in quality of life (QoL), as measured by Pediatric Functional

Assessment of Chronic Therapy (FACIT)

Fatigue questionnaire (patients * 5 years of age), from baseline to Day 183

(Week 26)

* 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)

* Percentage change in free hemoglobin from baseline to Day 183 (Week 26)

* 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,

major adverse vascular event [MAVE, including thrombosis], dysphagia, or

erectile dysfunction) in the

presence of elevated LDH as follows:

o For patients who enter the study naïve to complement inhibitor treatment,

elevated LDH * 2 × ULN after

prior LDH reduction to < 1.5 × ULN on therapy

o For patients who enter the study stabilized on eculizumab treatment, elevated

LDH * 2 × ULN

Safety

The safety and tolerability of ALXN1210 will be evaluated from baseline to Week

26 and throughout the extension

period by physical examinations, vital signs, physical growth,

electrocardiograms (ECGs), laboratory assessments,

and incidence of adverse events (AEs) and serious adverse events (SAEs). The

proportion of patients who develop

antidrug antibodies (ADAs) will also be assessed.

Study description

Background summary

PNH is an ultra-rare, debilitating, and life-threatening disease, driven by chronic uncontrolled complement activation.The resulting inflammation and cellular damage lead to systemic complications, principally through intravascular hemolysis and thrombophilia (Brodsky, 2014; Socie, 1996). PNH has an estimated worldwide incidence of 1.3 per million population (Hill, 2006). The onset of PNH is typically in adulthood, with pediatric cases accounting for < 5% of reported cases (Ware, 1991). Given the extremely small target population, studies of children with PNH have been limited to case reports, case series, and a small clinical trial (Reiss, 2005).

Patients with PNH are at risk of substantial morbidity and mortality and altered quality of life. The current standard of care for the treatment of PNH is eculizumab (Soliris®).The efficacy and safety of eculizumab for the treatment of PNH are well established. The approved dosage regimen for eculizumab for PNH involves 4 weekly induction doses, followed by maintenance doses administered every 2 weeks starting at Week 5.

Given that PNH is a chronic disease, the current eculizumab regimen may significantly affect patients, many of whom have to miss days of work or school to accommodate treatment. In some cases, patients may refuse treatment or be may be unable to comply with the treatment frequency of eculizumab. Practice survey research supports the assumption that the less frequent infusions associated with ALXN1210 will have a positive impact on daily life for patients and their caregivers.

In this Phase 3, open-label study, the PK, pharmacodynamics (PD), efficacy, and safety of ALXN1210 will be assessed in pediatric patients with PNH.

Study objective

The primary objective of this study is to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of ALXN1210 in pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH).

Study design

This is a Phase 3, open-label, single-arm multicenter study to evaluate the PK/PD, safety, and efficacy of ALXN1210 administered by intravenous (IV) infusion to pediatric patients (< 18 years of age) with PNH. The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period. Consenting patients will be screened for study eligibility up to 4 weeks prior to Day 1. Patients who satisfy all of the inclusion criteria and all of the exclusion criteria will be enrolled into the Primary Evaluation Period and receive a weight-based loading dose of ALXN1210 on Day 1, followed by weight-based maintenance treatment with ALXN1210 on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing * 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of treatment. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient*s last dose of eculizumab.

An interim analysis of data, including ALXN1210 PK and free complement component 5 (C5) levels, will be conducted after 4 patients weighing * 5 kg to < 40 kg have completed dosing through Day 71. Enrollment of patients will proceed without interruption while the analysis is ongoing. The accrued safety and PK/PD data will be assessed to ensure that ALXN1210 treatment is well tolerated and is providing adequate complement inhibition. Based on this review, the dose regimen may be adjusted.
In addition, an independent Data Monitoring Committee (DMC) will review safety data from the study on a regular basis.
After completion of all assessments on Day 183, all patients will enter an Extension Period and continue to receive ALXN1210 according to the appropriate weight-based regimen. The Extension Period will continue until the product is registered or approved (in accordance with country-specific regulations) or for up to 2 years, whichever occurs first. The end of trial is defined as the last patient*s last visit or follow-up (whether on site or via phone call) in the Extension Period.

Intervention

ALXN1210 loading doses on Day 1 and maintenance doses on Day 15 and q8w thereafter for patients weighing
* 20 kg, or q4w for patients weighing < 20 kg will be administered by IV infusion. Dosages are based on the
patient*s body weight recorded on dosing day or the most recently recorded weight, as shown in table 5 in the protocol (page 32)

Study burden and risks

This study includes a screening period, a treatment period, and an extension period. Participation in this study is anticipated to be approximately 2,5 years. The screening period will take up to 28 days, the

treatment phase will take 26 weeks and the extension period will last up to 2 years

In total, the patient will visit the hospital approximately between 22 and 35 times (depending if the weight is > 20 kg or below 20 kg).
The following tests and procedures will take place during the different visits:

9x completion of questionnaires about the general quality of life
15 x physical examination and assessment of PNH symptoms and vital signs
12x Pregnancy test (only for children who menstruate)
12x Urine sample collection
15x Blood samples collection
study medication dosing:
patients>-20 kg: max 21x
patients<20 kg: max 33x

If patients receive a supplemental dose of study drug, additional PK/PD samples will be collected and one additional physicial examination including vital signs will be done.

vaccinations:
- meningococcal vaccination if the patient has not been vaccinated before for PNH and the study doctor feels the patient is old enough
- vaccinations for influenzae type b (Hib) and Streptococcus pneumoniae if this is considered needed by the study doctor.

Please refer to the IB and patient information regarding side effects that are expected and for other risks and discomforts.

The current standard of care for the treatment of PNH is eculizumab (Soliris®). The efficacy and safety of eculizumab for the treatment of PNH are well established. The approved dosage regimen for eculizumab for PNH involves 4 weekly induction doses, followed by maintenance doses administered every 2 weeks starting at Week 5.

Given that PNH is a chronic disease, the current eculizumab regimen may significantly affect patients, many of whom have to miss days of work or school to accommodate treatment. In some cases, patients may refuse treatment or be may be unable to comply with the treatment frequency
of eculizumab. Practice survey research supports the assumption that the less frequent infusions associated with ravulizumab will have a positive impact on daily life for patients and their caregivers.

Serious side effects of the study drug ravulizumab:
Patients receiving ravulizumab, even after one dose, are at increased risk of developing a serious meningococcal infection (meningitis) caused by the bacteria Neisseria meningitidis. The infection can affect the tissues around

the brain and spinal cord (meningococcal meningitis) of can occur in blood (meningococcal sepsis). Meningococcal infections can rapidly become life-threatening or fatal, especially if not recognized and treated early. Patients may therefore be vaccinated against meningococcal infections. This vaccination alone may not be sufficient to prevent meningococcal infection. There is also a risk of getting other serious infections such as a gonococcal infection spread by the body through Neisseria gonorrhoeae.

Other side effects of study drug ravulizumab:
Very common side effects (seen in more than 10 % of the patients)
* Diarrhea
* Nausea
* Fever
* Tiredness
* Nasopharyngitis (swelling of the nasal passages and throat)
* Upper respiratory tract infection (common cold)
* Headache

Common side effects (seen in 1% to 10% of the patients)
* Abdominal pain
* Vomiting
* Indigestion
* Flu-like illness
* Weakness
* Muscle pain
* Muscle spasms
* Back pain
* Joint pain
* Dizziness
* Rash
* Itchiness
*
Uncommon side effects (seen in less than 1% of the patients):
* Chills

During the standard of care, patients visit the hospital every 1-3 months to check PNH and blood is drawn during these visits, physical examinations are done and any problems are discussed with the physician. If the child receives treatment for PNH, blood is drawn during each visit in the hospital and there is contact with the physician every 4-6 weeks. Where relevant, the study visits will be combined as much as possible with the regular visits. Additional procedures (like ECG, completion of questionnaires and additional blood draws) have been highlighted in the ICF in the schedule of events.

Contacts

Public
Alexion Pharmaceuticals

Seaport Boulevard 121
MA, Boston 02210
US
Scientific
Alexion Pharmaceuticals

Seaport Boulevard 121
MA, Boston 02210
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female patients < 18 years of age and weighing * 5 kg at the time of consent.
2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation of red blood cells (RBCs) and white blood cells (WBCs), with granulocyte or monocyte clone size of * 5%.
3. For patients not currently treated with complement inhibitor, presence of 1 or more of the following PNHrelated signs or symptoms within 3 months of Screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia, history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed RBC transfusion due to PNH.

4. Lactate dehydrogenase (LDH) values at Screening as follows:
a. For patients not currently treated with eculizumab, LDH level * 1.5 × upper limit of normal (ULN).
b. For patients who are currently taking eculizumab, LDH * 1.5× ULN (sample must be obtained on a
scheduled eculizumab-dosing day prior to dose administration [ie, at trough eculizumab level] and
analyzed by the central laboratory).
5. To reduce the risk of meningococcal infection (Neisseria meningitidis), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
6. Patients must have been vaccinated against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae according to national and local vaccination schedule guidelines, as appropriate.
7. Female patients of childbearing potential (ie, have achieved menarche) and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
8. Patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]) and comply with the study visit schedule.

Exclusion criteria

1. Platelet count < 30,000/mm3 (30 × 109/L) at Screening.
2. Absolute neutrophil count < 500/*L (0.5 × 109/L) at Screening.
3. History of bone marrow transplantation.
4. History of N. meningitidis infection.
5. History of unexplained, recurrent infection.
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
7. History of malignancy within 5 years of Screening with the exception of adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix.
8. 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 trial.
9. Unstable medical conditions (eg, myocardial ischemia, active

gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Screening, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol.
10. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
11. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
12. Females who plan to become pregnant or are currently pregnant or breastfeeding.
13. Females of childbearing potential who have a positive pregnancy test result at Screening or on Day 1.
14. Participation in another interventional treatment 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.
15. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
16. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Sponsor, might interfere with the patient*s full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-07-2018
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ultomiris
Generic name:	ravulizumab

Ethics review

Approved WMO Date:	10-01-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-03-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-002820-26-NL

Register	ID
CCMO	NL63627.041.17