A Randomized, Double-blind, Active-controlled, Phase 3 study evaluating the Efficacy and Safety of ABP 959 compared with Eculizumab in Adult Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Published: 02-11-2017
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Primary Objective: The primary objective for this study is to evaluate the efficacy of ABP 959 compared with that of eculizumab based on control of intravascular hemolysis.Secondary Objective: The secondary objective is to assess the safety,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50383

Source
ToetsingOnline

Brief title
DAHLIA

Condition

- Haematological disorders NEC

Synonym
Paroxysmal Nocturnal Hemoglobinuria, PNH

Research involving

Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen Inc.

Intervention

Keyword: eculizumab, Paroxysmal Nocturnal Hemoglobinuria, PNH

Outcome measures

Primary outcome

The primary objective for this study is to evaluate the efficacy of ABP 959

compared with that of eculizumab based on control of intravascular hemolysis.

Secondary outcome

The secondary objective is to assess the safety, pharmacokinetics (PK), and

immunogenicity of ABP 959 compared with that of eculizumab.

Study description

Background summary

ABP 959 is being developed as a *biosimilar* to eculizumab. This means that there are no meaningful clinical differences in terms of safety, purity and potency between the 2 products. The main difference between both drugs is that eculizumab is already approved for this use and can be prescribed, whereas the study drug ABP 959 cannot be prescribed yet because it is still being investigated.
The active ingredient of ABP 959 is a monoclonal antibody similar to eculizumab. Antibodies are made naturally in the body to defend against infections or against other foreign proteins. Eculizumab inhibits the immune system attacking the red blood cells.

Study objective

Primary Objective: The primary objective for this study is to evaluate the efficacy of ABP 959 compared with that of eculizumab based on control of

intravascular hemolysis.

Secondary Objective: The secondary objective is to assess the safety, pharmacokinetics (PK), and immunogenicity of ABP 959 compared with that of eculizumab.

Study design

This is a randomized, double-blind, active-controlled, 2-period crossover study in adult subjects with PNH. Approximately 40 subjects will be randomized (1:1) to receive each investigational product in 1 of 2 sequences, either treatment T followed by treatment R (TR) or treatment R followed by treatment T (RT).

Treatment will be administered over 2 periods: Period 1 will be 52 weeks in duration; Period 2 will start at week 53 with a crossover in treatment and will be 26 weeks in duration.

Period 1 (week 1 to week 53):
Treatment T: ABP 959 at a dose of 900 mg intravenously (IV) every 14 ± 2 days for 52 weeks
Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 52 weeks

Period 2: (week 53 to week 79)
Treatment T: ABP 959 at a dose of 900 mg IV every 14 ± 2 days for 26 weeks
Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 26 weeks

Subjects may require dose adjustment (ie, increase dose to 1200 mg) within the recommended 14 ± 2 day dosing schedule for investigational product based on signs and symptoms of intravascular hemolysis, including lactate dehydrogenase (LDH) levels.
Subjects will remain in the treatment phase until 14 days after the last planned dose of investigational product in Period 2 (ie, at week 79).
An independent data monitoring committee (DMC) will evaluate the safety data throughout the study.

Intervention

Period 1 (week 1 to week 53):
Treatment T: ABP 959 at a dose of 900 mg intravenously (IV) every 14 ± 2 days for 52 weeks
Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 52 weeks

Period 2: (week 53 to week 79)
Treatment T: ABP 959 at a dose of 900 mg IV every 14 ± 2 days for 26 weeks
Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 26 weeks

Study burden and risks

Disadvantages of participation in the study may be
* possible side effects/risks/discomforts of the treatment and/or procedures of the study;
* additional or longer hospital stays;
* additional tests;
* instructions to follow;

The information that is available on the possible side effects and/or risks of ABP 959 or eculizumab, is based on reports received from other people during their treatment with eculizumab. Since ABP 959 is a biosimilar, it is expected to have the same or very similar side effects as eculizumab. However, investigating the safety and side effects of ABP 959 is one of the main purposes of this study.

More information about eculizumab (including side effects/risks) can be found in the package leaflet of eculizumab..

The risks of ABP 959 and eculizumab on an unborn baby or a nursing infant are not yet known. Therefore, women who are breastfeeding or pregnant or are planning to become pregnant during the study or within 5 months after the last dose of study drug cannot be included in the study.

It is not known, if the study medication can potentially cause damage to the genetic material of the sperm, therefore male subjects should not father a child during their participation in the study and within 5 months after their last dose of study treatment. Subjects (including their partners) must use a highly effective form of birth control during this study and for at least 5 months after the last administration of either ABP 959 or eculizumab.

Treatment may reduce the patients natural resistance to infections, especially against certain organisms that cause meningitis (infection of the linings of the brain). Serious meningococcal infections have occurred in patients treated with eculizumab and may become rapidly life-threatening or result in death if not recognized and treated early. Please consult the patients doctor before a patient takes the study drug to be sure that the patient has received vaccination against Neisseria meningitidis, an organism that causes meningitis. The patient should have received this vaccination prior to starting the eculizumab treatment. Please confirm with the patients doctor that the patients current meningitis vaccination is up to date. Patients should also be aware that vaccination may not prevent this type of infection. In accordance with national recommendations, the patients doctor might consider that the patient needs supplementary measures to prevent infection.

More information about the possible side effects and risks of ABP 959 or

eculizumab and possible risks related to the procedures of the study can be found in appendix E of the ICF.

There may be risks or side effects related to the study drug or other study procedures that are unknown at this time. In addition, there may be possible side effects related to ABP 959 that are different from those of eculizumab that are unknown at this time. Subjects will be informed in a timely manner if new information on the study medication becomes available that may be relevant to continued participation in the trial.

The study treatment may help patients in the treatment of PNH but this cannot be guaranteed.
The efficacy and safety of eculizumab have been consistently shown in various clinical studies. As a result, eculizumab is indicated for use in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). Eculizumab is also approved for the treatment of patients with atypical Haemolytic Uremic Syndrome (aHUS). The current benefit-risk profile of ABP 959 is considered acceptable in the proposed study because ABP 959 has been shown to be similar to eculizumab in the quality analysis, pre-clinical and clinical phase 1 study, and the study design for the phase 3 trial is in accordance with current standard of care and is in line with current guidelines for the development of biosimilar medicines.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The study will enroll subjects with PNH who are stable on eculizumab treatment. Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed:
1. Men and women * 18 years of age
2. Historical diagnosis of PNH by documented flow cytometry
3. Administration of eculizumab for * 6 months and currently receiving 900 mg of eculizumab every 14 ± 2 days
4. Hemoglobin * 9.0 g/dL for at least 6 weeks prior to randomization
5. Lactate dehydrogenase (LDH) < 1.5 × the upper limit of normal at screening
6. Platelet count * 50 × 109/L
7. Absolute neutrophil count * 0.5 x 109/L (500/*L)
8. Subjects must be vaccinated against Neisseria meningitidis. Subjects must have been vaccinated or revaccinated according to current national guidelines for vaccination use.
9. Subjects must sign an institutional review board/independent ethics committee-approved informed consent form before participation in any procedures.

Exclusion criteria

If any of the following apply, the subject MUST NOT enter the study:
1. Known or suspected hereditary complement deficiency
2. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association * Class III], serious uncontrolled cardiac arrhythmia), peripheral vascular disease, cerebrovascular accident, or transient ischemic attack in the previous 6 months
3. Evidence of acute thrombosis (liver Doppler ultrasound of hepatic and portal veins)
4. Known to be positive for human immunodeficiency virus
5. Woman who is pregnant or breastfeeding
6. Woman of childbearing potential who does not consent to use a highly effective method of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 5 months after the last administration of

protocol-specified treatment
7. Man with a partner of childbearing potential who does not consent to use a highly effective method of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 5 months after the last administration of protocol-specified treatment
8. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or subject is receiving other investigational agent(s).
9. Subject has known sensitivity to any constituents of the products to be administered during the study, including mammalian cell-derived drug products.
10. History or evidence of clinically significant disorder, infection, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
11. History of meningococcal infection
12. Presence or suspicion of active bacterial infection, or recurrent bacterial infection.
13. History of bone marrow transplantation
14. Red blood cell transfusion required within 12 weeks before randomization
15. Subject experienced * 2 breakthrough events, (ie, signs and symptoms of intravascular hemolysis, that require dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-06-2019

Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABP 959
Generic name:	(biosimilar to) eculizumab
Product type:	Medicine
Brand name:	Soliris
Generic name:	eculizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-11-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	09-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2021
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	EUCTR2017-001418-27-NL
CCMO	NL62410.091.17