A Phase III, Randomized, Multi-Center, Open-Label, Active-Comparator Controlled Study to to Evaluate the Efficacy and Safety of APL-2 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

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The primary objectives of this study are to establish the efficacy and safety of APL-2 compared to eculizumab in patients with PNH who continue to have Hb levels

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

Summary

ID

NL-OMON46308

Source
ToetsingOnline

Brief title
PEGASUS

Condition

- Red blood cell disorders

Synonym
disease of the blood with a too quick destruction of red blood cells in the bloodstream

Research involving
Human

Sponsors and support

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

Intervention

Keyword: active-comperator, effiacy, PNH, safety

Outcome measures

Primary outcome

The primary objectives of this study are to establish the efficacy and safety

of APL-2 compared to eculizumab in patients with PNH who continue to have Hb

levels <10.5 g/dL despite treatment with eculizumab.

Primary Efficacy Endpoint

* Week 16 change from baseline in hemoglobin level

Secondary outcome

Secondary Efficacy Endpoints

* Week 16 change from baseline in reticulocyte count

* Week 16 change from baseline in lactate dehydrogenase (LDH) level

* Week 16 change from baseline in FACIT-fatigue scale score

* Number of PRBC units transfused from Week 4 to Week 16 (Day 28 to Day 112)

* Hemoglobin response in the absence of transfusions (Yes/No). Hemoglobin

response is defined as a 1g/dL increase in hemoglobin from Baseline at Week 16

* Reticulocyte normalization in the absence of transfusions at Week 16

(Yes/No). Reticulocyte normalization is defined as the reticulocyte count being

below the upper limit of the normal range

Study description

Background summary

Phase 1 clinical experience has demonstrated that APL-2 provides sustained inhibition of hemolytic activity in PNH patients who have never received eculizumab (Protocol APL2-CP-PNH-204, New Zealand) and in patients receiving eculizumab (Protocol APL-CP0514, US) who continue to be anemic (Hb <10.5 g/dL). To date, no safety signals have emerged from on-going studies in PNH patients that preclude further development. Thus, this proposed Phase 3 study*s aim is to confirm treatment efficacy and safety of APL-2 monotherapy for the treatment of PNH.

Study objective

The primary objectives of this study are to establish the efficacy and safety of APL-2 compared to eculizumab in patients with PNH who continue to have Hb levels <10.5 g/dL despite treatment with eculizumab.

Study design

This is a prospective, randomized, multi-center, open-label, active-comparator controlled study. A total of approximately 70 PNH patients who are receiving eculizumab and meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive either APL-2 or eculizumab. The treatment period of the study will consist of three parts: a 4-week run-in period, a 16-week randomized controlled period and a 32-week open-label APL-2 only period.
During the 4-week run-in period (Week -4 to Day -1) all subjects will receive self-administered twice-weekly subcutaneous doses of APL-2 1,080 mg in addition to the subjects* current dose of eculizumab treatment. On Day 1, subjects will receive their dose of APL-2 and may receive eculizumab depending on their dosing schedule. To account for variance in subject dosing schedules for eculizumab, subjects may receive their eculizumab dose on Day 1 or up to 4 days prior to Day 1. Subjects will then be randomized to either Group 1 (monotherapy APL-2) or Group 2
(monotherapy eculizumab). Subjects in Group 1 will receive APL-2, and subjects in Group 2 will receive eculizumab for the remainder of the 16-week randomized controlled period. During the randomized controlled period, subjects will return to the clinical site at Weeks 1, 2, 4, 6, 8, 12 and 16 for efficacy and safety assessments.
The randomization will be stratified by the following values:
* Number of units of PRBC transfused within the 12 months prior to Day -28 (<3 ; *3)
* Platelet count at screening (<100,000 ; *100,000)

Week 4 to Week 16 is defined as the active-comparator controlled period, over which endpoints are assessed. The wash-out period will take place over the first 4 weeks, i.e. withdrawal of eculizumab (Group 1) or APL-2 (Group 2) on Day 1 for 4 weeks.
After completion of the active-comparator controlled period (the end of Week 16), all subjects will continue into a 32-week open-label period during which all subjects will receive twice-weekly doses of APL-2 1,080 mg. During this period, subjects will return to the clinical site on Weeks 17, 18, 20, 22 and 24 and every 4 weeks thereafter until Week 48 for efficacy and safety assessments. Those subjects who received eculizumab in the randomized controlled period will receive APL-2 in addition to eculizumab for 4 weeks (Weeks 17-20). The wash-out period will then occur over the next 4 weeks (Weeks 21-24).
After completion of the 52-week treatment period (Week 48), subjects will be offered entry into an open label extension study. Should the subject not enter the open label extension study they will exit the study and return to the site for 2 additional safety visits 6 weeks apart.
Subjects who withdraw from treatment prior to the Week 48 visit will be encouraged to continue their participation in the study and return to the study site for their scheduled study procedures, with the exception of APL-2 administration. Subjects who withdraw from the study prior to Week 48 and are currently being treated solely with APL-2 are recommended to receive at least one dose of eculizumab before discontinuing APL-2.
An external, independent Data and Safety Monitoring Board (DSMB) will assess the progress and cumulative safety/tolerability data of the study.
Subjects who fail the screening procedures should not be re-screened for the study unless this is agreed in advance and documented in writing with the sponsor.

Intervention

Group 1 :APL2
* 1,080 mg twice weekly
o Dose adjustment to 1,080mg every 3 days if required
* Subcutaneous infusion

* Group 2: Eculizumab :
The dose of eculizumab will remain the same as dose patients received prior to entering this trial. Intravenous.

Study burden and risks

Possible risks, side effects, and discomforts include:
* Infections - pt may be at increased risk for infections caused by certain types of organisms such as Streptococcus pneumonia, Neisseria Meningitidis, or Haemophilus influenza.

Symptoms include:
o Fever
o Headache
o Stiff neck
o Nausea
o Vomiting
o Eye sensitivity to light
o Confusion
* Allergic reactions - all medications have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.
o Rash
o Fast pulse
o Sweating
o Feeling of dread
o Swelling around the eyes and mouth
o Swelling of the throat
o Wheezing
o Having a hard time breathing
o Sudden drop in blood pressure (making you feel dizzy or lightheaded)
o Inability to breathe without assistance
* Blood samples - pt may have discomfort or pain when your blood is collected. pt may feel faint or pass out. There is also a slight possibility of infection, bruising, or bleeding at the puncture site.
* ECG - skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
* Antibiotic therapy - In the event that the study doctor decides that pt has to take antibiotics throughout the study, there is a possibility that pt will experience some side effects from the antibiotic treatment.
* Infusion site reactions - there is a possibility that pt could experience redness, swelling, and pain or tenderness at the site of infusion. There is also a slight possibility of infection.
* Vaccination - Like any medication, vaccines can cause side effects. The side effects associated with getting vaccines are almost always mild (such as redness and swelling where the shot was given) and usually go away within a few days.
* Since the study drug (APL-2) is investigational, when taken alone or in combination with other medications, there may be other risks that are unknown.

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

2. Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry
3. On treatment with eculizumab. Dose of eculizumab must have been stable for at least 3 months prior to the Screening Visit
4. Hb <10.5 g/dL at the Screening Visit
5. Absolute reticulocyte count > 1.5x ULN at the Screening Visit
6. Platelet count of >50,000/mm3 at the Screening Visit
7. Absolute neutrophil count >500/mm3 at the Screening Visit

Exclusion criteria

1. Active bacterial infection within 4 weeks prior to Day -28 (Run-in Period)
2. Receiving iron, folic acid, vitamin B12 and EPO, unless the dose is stable, in the 4 weeks prior to Screening
3. Hereditary complement deficiency
4. History of bone marrow transplantation
5. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration
6. Participation in any other investigational drug trial or exposure to other investigational

agent within 30 days or 5 half-lives (whichever is longer)
10. Myocardial infarction, CABG, coronary or cerebral artery stenting and /or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or greater than Class 2 Angina Pectoris or NYHA Heart Failure Class >2
11. QTcF > 470 ms, PR > 280 ms
12. Mobitz II 2nd degree AV Block, 2:1 AV Block, High Grade AV Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator (ICD) with backup pacing capabilities
13. Receiving Class 1 or Class 3 antiarrhythmic agents, or arsenic, methadone, ondansetron or pentamidine at screening

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:	APL2
Generic name:	pegcetacoplan (proposed)
Product type:	Medicine
Brand name:	Soliris
Generic name:	Eculizumab

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-05-2019
Application type:	First submission
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	EUCTR2017-004268-36-NL
ClinicalTrials.gov	NCT03500549
CCMO	NL66816.091.18