An Open Label, Single Arm Study to Evaluate the Efficacy and Safety of REGN3918 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Are Complement Inhibitor Naive or Have Not Recently Received Complement Inhibitor Therapy

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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-OMON48163

Source
ToetsingOnline

Brief title
Study in patients with PNH not treated previously with Complement Inhibitor

Condition

- Red blood cell disorders

Synonym
Marchiafava□Micheli syndrome, stem cell disorder

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Phase 2, PNH, REGN3918

Outcome measures

Primary outcome

- The proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH * 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive

- The proportion of patients achieving transfusion avoidance defined as no post baseline transfusion of RBCs per protocol through week 26

Secondary outcome

- The rate of breakthrough hemolysis through week 26, defined as the measurement of LDH * 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (ie, LDH * 1.5 x ULN)

- The proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH * 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive

- Time to first LDH * 1.5 x ULN

- Percentage of days with LDH * 1.5 x ULN between week 4 and week 26, inclusive

- Change and percent change in LDH levels from baseline to week 26

- The rate and number of units of transfusion with RBCs through week 26

- Change in RBC hemoglobin levels from baseline to week 26

- Change in free hemoglobin levels from baseline to week 26

- Change and percent change in total complement hemolytic activity assay (CH50) from baseline to week 26

- Change in patient-reported outcomes (fatigue as measured by the FACIT-Fatigue and health-related quality of life as measured by the European Organization for Research and Treatment of Cancer [EORTC]-QLQ-30 and EQ-5D-3L) from baseline to week 26

- Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables through week 26

- Concentrations of total REGN3918 in serum assessed throughout the study

- Incidence of treatment-emergent anti-drug antibodies to REGN3918 in patients over time

Study description

Background summary

Eculizumab, approved for the treatment of PNH in many countries worldwide, is a humanized monoclonal antibody directed against the terminal complement protein C5. It blocks the formation of the MAC - C5b-9,thus protecting PNH RBCs from complement-mediated intravascular hemolysis. The basis for approval of eculizumab has been its effectiveness in PNH, as evidenced by the initial reduction of lactate dehydrogenase (LDH) levels and by the long-term reduction in the need for blood transfusions; decrease in the incidence of thrombosis; improvement in anemia; and improvement in quality of life.
However, not all patients receive optimal therapeutic benefit. For example, 25% of patients still need recurrent, albeit less frequent, blood transfusions. Up to 20% of patients on eculizumab
therapy require significant increases in dose or dose frequency due to

breakthrough hemolysis secondary to incomplete inhibition of C5. In rare instances, eculizumab is ineffective due to polymorphic variation in the gene encoding C5 such that the protein is not recognized by eculizumab. The heterogeneity in these hematological responses may be related to underlying aplastic anemia, C3b-mediated extravascular hemolysis, or incomplete pharmacologic blockade of C5, and rare polymorphisms in the gene coding for C5. Eculizumab administration every 2
weeks (Q2W) by intravenous (IV) infusion has been described as burdensome for patients.

REGN3918 is anticipated to provide better control of breakthrough hemolysis by providing maximal and durable inhibition of C5 throughout the dosing interval, improving the dosing
regimen, binding to the polymorphic variant C5 protein which renders eculizumab ineffective, and development of a convenient subcutaneous formulation.

Study objective

The primary objective of the study is to demonstrate a reduction in intravascular hemolysis by REGN3918 over 26 weeks of treatment in patients with active PNH who are treatment-naive to complement inhibitor therapy or have not recently received complement inhibitor therapy.

The secondary objectives of the study are:
- To evaluate the safety and tolerability of REGN3918.
- To evaluate the effect of REGN3918 on parameters of intravascular hemolysis
- To assess the concentrations of total REGN3918 in serum.
- To evaluate the incidence of treatment-emergent anti-drug antibodies to REGN3918.
- To evaluate the effect of REGN3918 on patient-reported outcomes (PROs) measuring fatigue and health-related quality of life

Study design

This is an open-label, single arm, 26-week treatment study in patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor naïve or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit.

In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Dose confirmation will be made at the interim analysis. The inclusion and exclusion criteria and schedule of events are the same for cohort A and cohort B. During the assessment of data from cohort A, recruitment into the study will continue, with patients recruited being assigned subsequently as follows: if a decision is made to expand cohort A, they will be assigned to cohort A. If a decision is made to progress to

cohort B, they will be assigned to cohort B.

Patients will be given a single loading dose of REGN3918 30 mg/kg intravenous (IV) on day 1, then a dose not greater than 800 mg subcutaneous (SC) once weekly (QW; ± 1 day) to week 26.

Intervention

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Study burden and risks

-Additional visits to the hospital, additional physical tests, including a test for gonnorhea and pregnancy.
-Possible rash or superficial irritation of the skin by the ECG stickers.
-In total about 600 ml blood will be taken, divided over 10 visits (Part A/B and C). This amount won't cause any problems (to compare: a blood donation involves 500ml of blood being taken each time). Possible side effects of blood tests or biopsies are fainting, contusions, sore spot and sensitive area at the injection site and, in rare cases, an infection.

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

- Male or female * 18 years of age or legal age of majority at screening, whichever is greater
- Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by high-sensitivity flow cytometry
- Active disease, as defined by the presence of 1 or more PNH-related signs or symptoms or history of red blood cell (RBC) transfusion due to PNH within 3 months of screening.
- Lactate dehydrogenase (LDH) level * 2 × upper limit of normal (ULN) at screening visit.
- PNH granulocytes (denoted as polymorphonuclear [PMN]) >10% at screening visit.

Exclusion criteria

Prior treatment with a complement inhibitor either within 6 months prior to screening visit or at any time where the patient was refractory to complement inhibitor therapy, in the opinion of the investigator (with the exception of eculizumab refractory patients due to the C5 variant R885H/C)

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	REGN3918
Generic name:	REGN3918

Ethics review

Approved WMO Date:	02-04-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-03-2020
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-08-2020
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	EUCTR2018-002734-20-NL
CCMO	NL69110.091.19
Other	not yet known