A Randomized, Open-Label, Multicenter, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria in Subjects with Inadequate Response to C5 Inhibitor Therapy

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Part 1 - To determine the efficacy of oral BCX9930 monotherapy administered for 24 weeks, compared to continued complement component 5 (C5) inhibitor therapy, in subjects with paroxysmal nocturnal hemoglobinuria (PNH) with an inadequate response to...

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

Summary

ID

NL-OMON51609

Source
ToetsingOnline

Brief title
REDEEM-1

Condition

- Red blood cell disorders

Synonym
paroxysmal nocturnal hemoglobinuria, PNH

Research involving
Human

Sponsors and support

Primary sponsor: BioCryst Pharmaceuticals Inc
Source(s) of monetary or material Support: BioCryst Pharmaceuticals Inc

Intervention

Keyword: PNH

Outcome measures

Primary outcome

Part 1-

Change from baseline (CFB) in hemoglobin (Hb) [mean of values at Weeks 12, 16,

20, and 24]

Part 2 -

Number and proportion of subjects with a TEAE

Number and proportion of subjects who discontinue due to a TEAE

Number and proportion of subjects who experience a TESAE

Number and proportion of subjects who experience a CTCAE Grade 3 or Grade 4 TEAE

Number and proportion of subjects who experience a treatment-emergent CTCAE

Grade 3 or Grade 4 laboratory abnormality

Secondary outcome

Part 1 -

1. Proportion of subjects who are transfusion-free [from week 4 to Week 24]

2. Number of units of packed red blood cells (pRBCs) transfused [from week4 to

Week 24]

3. CFB in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]

Part 2

CFB in Hb [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

Proportion of subjects with Hb >= 12 g/dL [at Week 52]

Proportion of subjects with Hb stabilization (avoidance of a > 2 g/dL decrease in the absence of transfusion) [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Week 28 to Week 52 for subjects randomized to continue C5 inhibitor]

Proportion of subjects who are transfusion-free [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]

Number of units of pRBCs transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 26 to 52 for subjects randomized to continue C5 inhibitor]

Percent reduction in the rate of pRBC units transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor vs. prestudy transfusion rate]

Percent CFB in LDH [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

CFB in ARC [mean of values from Weeks 28 to 52 for subjects randomized to

BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

Proportion of subjects with ARC in the normal range [at Week 52]

CFB in haptoglobin [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

Proportion of subjects with haptoglobin >= LLN [at Week 52]

CFB in C3-opsonized RBCs [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

CFB in total PNH RBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

CFB in ratio of total PNH RBC clone size to PNH WBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

Study description

Background summary

PNH is a rare disease which causes patients to suffer from haemolysis, both intravascularly IVH (blood vessels) and extravascularly EVH (outside blood vessels, other organs). This results thrombosis, chronic anaemia and bone marrow failure.
PNH patients who are receiving the standard of care, a C5 inhibitor, can still experience uncontrolled disease, with low haemoglobin levels and often a continued need for transfusions. The clinical trial BCX9930-202 will investigate if, in PNH patients, BCX9930 oral therapy is better than C5

inhibitor
treatment (given via iv infusions), over a 24 week period, followed by a 28 week treatment period with all patients on BCX9930 to assess long term safety and tolerability.
This study will assess a new oral treatment BCX9930 with a different mode of action to the current standard of care (C5 inhibitors).

Study objective

Part 1 - To determine the efficacy of oral BCX9930 monotherapy administered for 24 weeks, compared to continued complement component 5 (C5) inhibitor therapy, in subjects with paroxysmal nocturnal hemoglobinuria (PNH) with an inadequate response to C5 inhibitor therapy

Part 2 - To evaluate the long-term safety and tolerability of oral BCX9930 monotherapy administered over a 28- to 52 week treatment period in subjects with PNH with an inadequate response to C5 inhibitor therapy

Study design

A randomized, active-controlled, open-label, multicenter, parallel group, 2-part study. Parts 1 and 2 will be conducted in the same subjects

Intervention

In Part 1, either continued C5 inhibitor therapy or BCX9930 monotherapy for 24 weeks. In Part 2, all subjects will receive BCX9930 monotherapy for 28 weeks.
Part 1 - C5 - n=27
Part 1 - BCX9930 - n=54
Part 2 - BCX9930 - n=81

BCX9930 will be administered orally at a dose of 200 mg BID, approximately 12 hours apart for 14 days increased to 400mg BID, using tablets.

Study burden and risks

A screening period of up to 4 weeks
A comparator treatment period of 24 weeks (Part 1) and a monotherapy extension period of 28 weeks (Part 2).

Based on 25 visits, the burden will be as follows:
Physical examinations, ECGs, Vital functions, blood tests, pregnancy tests, questionnaires. Vaccination if applicable: before the study and depending on previous vaccinations
Side effects of research medication and inconvenient research procedures.

Contacts

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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, aged >= 18 years old.
2. Body weight >= 40 kg.
3. Documented diagnosis of PNH confirmed by flow cytometry with a PNH granulocyte or monocyte clone size of >= 10% during screening.
4. Treated with a stable regimen of eculizumab for >= 3 months prior to the screening visit or ravulizumab for >= 6 months prior to the screening visit.
5. Recorded the following results during screening:
a. Hb of <= 105 g/L (<= 10.5 g/dL).
b. ARC of >= 100 × 10^9 cells/L (>= 100,000 cells/µL; >= 100 G/L).
c. Absolute neutrophil count of >= 0.75 × 10^9 cells/L (>= 750 cells/µL; >= 0.75 × G/L).
d. Platelet count of >= 30 × 10^9/L (>= 30,000/µL; >= 30 G/L).

e. Adequate iron reserve based on ferritin >= LLN or total iron binding capacity <= upper limit of the normal reference range (ULN).
f. Estimated glomerular filtration rate of >= 60 mL/min/1.73 m2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010).
6. Contraception requirements: WOCBP and partners of male subjects to use highly effective contraception
7. Documentation of current vaccinations against Neisseria meningitidis types A, C, W, and Y, and Streptococcus pneumoniae, or willingness to start vaccination series at least 14 days prior to Day 1.
(Note: Vaccination for N. meningitidis type B and for H. influenzae type B (Hib) is strongly encouraged where authorized and available.)
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the study, including compliance with the BID dosing schedule for BCX9930.
9. Willing and able to provide written informed consent

Exclusion criteria

1. Known history of or existing diagnosis of hereditary complement deficiency.
2. History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
3. Myocardial infarction or cerebrovascular accident within 30 days prior to screening, or current and uncontrolled clinically significant cardiovascular or cerebrovascular condition, including unstable angina, severe congestive heart failure, unexplained syncope, arrhythmia, and critical aortic stenosis.
4. History of malignancy within 5 years prior to the screening visit, with exception of adequately treated non-melanoma skin or superficial bladder cancer, curatively treated carcinoma in situ of the cervix, or other curatively treated solid tumor deemed by the investigator and medical monitor to be at low risk for recurrence.
5. Active bacterial, viral, or fungal infection or any other serious infection within 14 days prior to screening.
(Note: Suspected or confirmed coronavirus disease [COVID-19]; persistent or recurrent positive test(s) for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] nucleic acids or antigens; and worsening of dyspnea not due to PNH, vasculitic rash, and persistent fever or other symptoms consistent with multisystem inflammatory syndrome in adults [MIS A] are exclusionary.)
6. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
7. Treatment with anti-thymocyte globulin within 180 days prior to the screening visit.
8. Initiation of treatment with an erythropoiesis-stimulating agent (eg,

erythropoietin), a thrombopoietin receptor agonist (eg, eltrombopag), or danazol within 28 days prior to the screening visit.
(Note: Treatment with these medications initiated > 28 days prior to the screening visit is not exclusionary, if the dose is stable and there is a reasonable expectation that treatment will be continued.)
9. Receiving iron supplementation with an unstable dose in the 28 days prior to the screening visit.
10. Clinically significant abnormal electrocardiogram (ECG) at the screening visit.
(Note: This includes, but is not limited to, a QT interval corrected using Fridericia*s method [QTcF] of > 450 msec in males or > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.)
11. Subjects with any of the following results at the screening visit:
a. Alanine aminotransferase (ALT; also serum glutamic-pyruvic transaminase [SGPT]) >3 × ULN.
b. Aspartate aminotransferase (AST; also serum glutamic-oxaloacetic transaminase [SGOT]) >3 × ULN.
(Note: Subjects may be enrolled with AST >3 × ULN if explained by hemolysis.)
c. Total serum bilirubin >2 × ULN
(Note: Subjects may be enrolled with total serum bilirubin >2 × ULN if explained by hemolysis or Gilbert*s syndrome. In the case of hemolysis, total serum bilirubin must be <5 × ULN and in the case of Gilbert*s syndrome, total serum bilirubin must be <11 × ULN.)
12. Current use of a prohibited concomitant medication within 7 days prior to Day 1 as detailed in Section 9.8.1.
13. Positive serology for human immunodeficiency virus, or active infection with hepatitis B virus or hepatitis C virus, unless receiving antiviral therapy and viral load is undetectable.
14. Positive drugs of abuse screen, unless by prescription.
15. Pregnant, planning to become pregnant, or breastfeeding.
16. Known hypersensitivity to BCX9930 or any of its formulation excipients.
17. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.
18. Any other clinically significant medical or psychiatric condition that, in the opinion of the investigator or sponsor, would interfere with the subject*s ability to participate in the study or increase the risk of participation for that subject.

Study design

Design

Study phase:	2
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:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BCX9930
Generic name:	BCX9930
Product type:	Medicine
Brand name:	Soliris
Generic name:	eculizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ultomiris
Generic name:	Ravulizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2022
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	EUCTR2020-004438-39-NL
ClinicalTrials.gov	NCT05116774
CCMO	NL79892.091.21