A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF BIVV009 IN PATIENTS WITH PRIMARY COLD AGGLUTININ DISEASE WITHOUT A RECENT HISTORY OF BLOOD TRANSFUSION

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Primary Objective:The purpose of Part A is to determine whether sutimlimab administration results in a greater than or equal to (>=)1.5 gram per deciliter (g/dL) increase in hemoglobin (Hgb) level and avoidance of transfusion in participants with...

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

Summary

ID

NL-OMON55483

Source
ToetsingOnline

Brief title
Cadenza

Condition

- Haemolyses and related conditions
- Autoimmune disorders

Synonym

PRIMARY COLD AGGLUTININ DISEASE

Research involving
Human

Sponsors and support

Primary sponsor: Bioverativ USA Inc.
Source(s) of monetary or material Support: Sponsor Bioverativ USA Inc.

Intervention

Keyword: BIVV009, Double-blind, Open-Label, Primary Cold Agglutinin Disease, Randomised

Outcome measures

Primary outcome

Part A: Percentage of Participants With Response (R). A participant will be considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 (EOT) and did not receive treatment for primary cold agglutinin disease (CAD) beyond what ispermitted per protocol. Additionally, the participant's hemoglobin (Hgb) level must meet the following criterion: Hgb increase greater than or equal to (>=) 1.5 gram per deciliter (g/dL) from baseline (defined as the last Hgb value before administration of the first dose of study drug).

Part B: Number of Participants With Treatment-emergent Adverse Events (AEs) and Serious AEs (SAEs). An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship.

Secondary outcome

Part A:

1. Mean Change From Baseline in Hemoglobin (Hgb) Level up to Week 26.

2. Mean Change From Baseline in Bilirubin up to Week 26.

3. Mean Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score (Quality of Life).

FACITFatigue scale consists of 13 questions assessed using a 5 point scale (0=not at all; 1 = a little bit, 2 = somewhat, 3 = quite a bit and 4 = very much). Responses to each question are added to obtain a total score. The range of possible scores is 0-52, with higher score indicating more fatigue.

4. Mean Change From Baseline in Lactate Dehydrogenase (LDH) up to Week 26.

5. Percentage of Participants With Solicited Symptomatic Anemia at End of Treatment (EOT). Symptomatic anemia is defined as fatigue, weakness, shortness of breath, palpitations, fast heart beat, light headedness, and/or chest pain.

Part B:

6. Mean Change From Week 27 in Hemoglobin (Hgb) Level.

7. Mean Change From Week 27 in Bilirubin (total).

8. Mean Change From Week 27 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score (Quality of Life). FACITFatigue scale consists of 13 questions assessed using a 5 point scale (0=not at all; 1 = a little bit, 2 = somewhat, 3 = quite a bit and 4 = very much). Responses to each question are added to obtain a total score. The range of possible scores is 0-52, with higher score indicating more fatigue.

9. Mean Change From Week 27 in five level EuroQol five dimensions questionnaire (EQ-5D-5L). The EQ-5D descriptive system comprises 5 dimensions: mobility,

self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has a 5-level response: no problems, slight problems, moderate problems, severe problems, and extreme problems. A scale with score 0-100 is used to collect response on current health status. Higher the score better the health.

10. Mean Change From Week 27 in 12-item short form survey (SF-12). SF-12 health survey is a self-reported questionnaire to measure participant's profile of functional health and well-being. It includes 12 questions (Q).

11. Patient's Global Impression of [Fatigue] Severity (PGIS) total score in different timepoints. PGIS is a 5-point response to the severity of the fatigue over the past weeks where 1 indicates "no fatigue" to 5 as "very severe". The assessments will be performed every 3 months beginning after Week 27 up to Week 77.

12. Patient's Global Impression of Change (PGIC) total score in different timepoints. PGIC is a 7-point response to the change of overall status of quality of life where 1 indicates "Very much improved" to 7 as "very much worse". The assessments will be performed every 3 months beginning after Week 27 up to Week 77.

13. Mean Change From Week 27 in Lactate Dehydrogenase (LDH) level.

14. Number of transfusions.

15. Mean Change From Week 27 in Haptoglobin.

16. Number of healthcare visits by type. Number of healthcare visits by type such as office visit, hospital ER visit, hospitalization, and ICU stay will be

reported for the approximately 1 year duration of Part B.

Study description

Background summary

The CP has been implicated in many diseases that are driven by the presence of a pathogenic antibody; CAgD is one such example. Complement inhibition has proven to be a safe and effective treatment for another form of hemolytic anemia, paroxysmal nocturnal hemoglobinuria. Currently, there are approved complement inhibitors being used therapeutically for various indications, including Soliris® (eculizumab), a mAb targeting C5; Berinert® and Cinryze®, both C1 esterase inhibitors purified from human plasma; and Ruconest®, a recombinant form of human C1 esterase inhibitor. Unlike Soliris and the C1 esterase inhibitors, by specifically targeting C1s, BIVV009 inhibits only the CP, leaving the alternative complement pathway and the lectin complement pathway available for immune surveillance. Furthermore, by blocking at the level of the C1 complex, BIVV009 is expected toprevent generation of all anaphylatoxins and opsonins (eg, C3 fragments) that produce pathologic lesions in CP-mediated disorders.
CAgD is an autoimmune hemolytic anemia caused by IgM-induced CP activation, which is typically triggered by exposure to cold environmental temperatures or viral infections (Arthold et al. 2014; Berentsen 2011; Berentsen 2014; Berentsen et al. 2007; Petz 2008; Swiecicki et al. 2013). CAgD is typically not responsive to treatment with steroids or splenectomy and can only be managed by supportive measures (avoidance of cold, blood transfusions as needed), and/or immunosuppressive, cytotoxic therapies (eg, rituximab with or without fludarabine or bendamustine). A Phase 1b clinical trial of BIVV009 in patients with CAgD showed that it can rapidly induce complete remission of anemia (Jager and Gilbert 2016).

Study objective

Primary Objective:
The purpose of Part A is to determine whether sutimlimab administration results in a greater than or equal to (>=)1.5 gram per deciliter (g/dL) increase in hemoglobin (Hgb) level and avoidance of transfusion in participants with primary cold agglutinin disease (CAD) without a recent history of blood transfusion.
The purpose of Part B is to evaluate the long-term safety and tolerability of sutimlimab in participants with primary CAD.

Secondary Objective:
Part A:

To assess the effect of BIVV009 on clinical events and laboratory parameters related to hemolysis and anemia in patients with primary CAgD
To assess the effect of BIVV009 on specific complications of CAgD (acrocyanosis, Raynaud's syndrome, hemoglobinuria, and thromboembolism)
To assess the effect of BIVV009 on quality of life (QOL) in patients with primary CAgD
Part B:
The secondary objective of Part B is to investigate the durability of response during long-term treatment with BIVV009 in patients with primary CAgD.

Study design

This randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy, safety, and tolerability of BIVV009 in symptomatic patients with the complement-mediated disorder primary CAgD who do not have a recent history of blood transfusion.
During the 6-week Screening/Observation Period, prospective patients will have a detailed medical history documented (including all available transfusion history), physical evaluations, and blood samples collected for characterization of CAgD biomarkers, including Hgb levels on 3 occasions approximately every 2 weeks.
Patients under screening for Cadenza who require a transfusion(s) during the Screening/ Observation Period prior to the first study drug infusion (if medically indicated per the Investigator*s discretion and within the parameters of the protocol specified transfusion criteria, see Table 1) will be screen failed for Cadenza and enrolled into the Cardinal trial if they meet all the other study-specific entry criteria.
Part A
The study will enroll 40 primary CAgD patients who do not have a recent history of blood transfusion (ie, no transfusion during the last 6 months prior to enrollment), or who are newly diagnosed with an indeterminate transfusion history (ie, less than a 6-month history with no transfusions), or no transfusion history.
Eligible patients will be randomized 1:1 to receive an intravenous (IV) infusion of BIVV009 or placebo over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25 (ie, Days 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175). Patients who miss a dose (ie, outside the dosing window or > 17 days

since last
dose) should return to the site for an unscheduled visit to receive another loading dose
prior to their next scheduled visit. Patients will have an End of Treatment (EOT) visit in
Part A on Day 182 (Week 26).
Patients who meet the transfusion criteria in Table 1 during the 6-month double-blind
treatment period will receive a transfusion.
Table 1: Transfusion Criteria
A patient will receive a transfusion during Part A if his or her Hgb level meets either
of the following criteria:
* Hgb is < 9 g/dL and the patient is symptomatic, or
* Hgb is < 7 g/dL and the patient is asymptomatic
A responder analysis will be conducted following completion of the EOT visit at Week 26. The responder definition is provided in Table 2.
Table 2: Responder Definition
A patient will be considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 (EOT) and did not receive treatment for CAgD beyond what is permitted per protocol. Additionally, the patient*s Hgb level
must meet the following criterion:
* Hgb increase * 1.5 g/dL from baseline (defined as the last Hgb value before administration of the first dose of study drug) at treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26)
Note: Any patient withdrawing from the study after Week 5 and prior to the Week 23
visit will be considered a non-responder.
A list of excluded concomitant medications, as well as allowed concomitant medications
with restrictions, is provided in the protocol. Beyond the permitted concomitant medications, study drug, and transfusions, patients may receive no other therapies for the
treatment of CAgD while enrolled in Part A of this study; patients requiring other
treatment for their CAgD in Part A will be withdrawn from the study and counted as
non-responders.
Part B
Following completion of dosing in the initial 6-month treatment period, patients will roll
into the long-term safety and durability of response extension phase and receive BIVV009 in an open-label manner. Part B will run for approximately 1 year following
LPO under Part A.
Blinding will be maintained when rolling patients into the extension period by

providing
a crossover dose at Week 26 to allow placebo patients to receive the BIVV009 loading
dose at start of BIVV009 dosing. Patients who were randomized to BIVV009 during the
6-month treatment period will receive a placebo dose at Week 26 to maintain blinding.
All patients will then continue to receive BIVV009 dosing every 2 weeks starting at
Week 27. Should patients deviate from their scheduled dosing, a repeat loading dose
may be required. Optional in home visits may be utilized in Part B to ease the patient*s
travel burden; however, on-site visits will be completed ~ every 3 months (at a
minimum) for collection of pharmacodynamic (PD) and pharmacokinetic (PK) samples, ADA samples
and additional safety and efficacy measures. PK, PD and anti-drug antibodies (ADAs)
samples will be collected 9 weeks after administration of the last dose of study drug in
patients who discontinue early, as well as in patients who experience a hematological
breakthrough event.

Intervention

All patients will receive the following interventions:
- ECG
- Blood draws for safety (chemistry and hematology)
- Blood draws for pharmacokinetic parameters
- Bone marrow biopsy if needed
- Study drug will be administered over approximately 60 minutes by IV infusion in accordance with the Pharmacy Manual. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval.

Study burden and risks

2.2.4. Potential Risks and Benefits
As previously noted, clinical proof of concept for BIVV009 was achieved in a Phase 1b study,
which demonstrated immediate cessation of hemolysis and rapid correction of anemia during
short-term treatment of patients with CAgD.
The human safety risk from off-target effects of mAb therapeutics is generally considered to be
low, and in this regard BIVV009 is no exception. The human safety risk from

short-term
inhibition of the complement system also appears to be low, based upon the experience with five
approved products in this therapeutic class. Long-term, complement inhibition may increase the
risk of infection with encapsulated bacteria, as reflected in the product label for eculizumab
(Soliris), an inhibitor of the terminal portion of the complement system. However, this risk can
be mitigated with an appropriate program of prophylactic vaccinations, which has been
incorporated into the design of this study.
The risks associated with long-term inhibition of the proximal portion of the CP are presently
unknown. Theoretically, it could increase the risk of SLE or circulating immune complexes
(CIC) disease due to the role of the C1 complex in immune complex clearance, as observed in
patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). However,
pharmacologic inhibition of C1s differs from congenital deficiency of the C1 complex because:
1) congenital C1 complex component deficiency are commonly not single gene mutations but
typically are associated with second mutations in other immune system genes; 2) pharmacologic
inhibition of C1s enzymatic function in the C1 complex leaves intact the non-enzymatic function
of C1q, which is important for the opsonization and phagocytic removal of apoptotic cells which
protects against autoimmunity; and 3) the phenotype associated with life-long, often total
absence of C1 complex structure and function is unlikely to be reproduced by pharmacologic
antagonism of C1 enzymatic function in fully developed adults. Nevertheless, standard clinical
biomarkers related to SLE (eg, antibodies to double-stranded DNA [dsDNA]) have been
incorporated into the study design as safety surveillance measures.
Home infusions with the study drug will be proposed to a number of patients in countries pre-selected to participate in home infusion (including The Netherlands). Home infusions will be assisted by a trained healthcare professional, and will concern patients who express such wish, after having been qualified by the Investigator and no sooner than after Week 41 (Day 287) and without evidence of intolerance of the study drug as determined by the Investigator based on the criteria outlined in Appendix K (Appendix K of the protocol).

The overall risk/benefit balance for participants in Study BIVV009-04 is favorable based on
available data to date.

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

* Body weight of greater than or equal to (><=) 39 kilogram (kg) at Screening
* Confirmed diagnosis of primary cold agglutinin disease (CAD) based on the following criteria: a) Chronic hemolysis, b) Polyspecific direct antiglobulin test (DAT) positive, c) Monospecific DAT strongly positive for C3d, d) Cold agglutinin titer ><= 64 at 4 degree Celsius, and e) Immunoglobulin G (IgG) DAT less than or equal to (<<=) 1+, and, f) No overt malignant disease
* Hemoglobin level <<= 10.0 gram per deciliter (g/dL)

* Bilirubin level above the normal reference range, including patients with Gilbert's Syndrome

Exclusion criteria

* Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy
* Clinically relevant infection of any kind within the month preceding enrollment (example, active hepatitis C, pneumonia)
* Clinical diagnosis of systemic lupus erythematosus (SLE); or other autoimmune disorders with anti-nuclear antibodies at Screening. Antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis during the Confirmatory Review of Patient Eligibility
* Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody) prior to or at Screening
* Positive human immunodeficiency virus (HIV) antibody at Screening
* Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (example, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrollment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2018
Enrollment:	6

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BIVV009
Generic name:	BIVV009

Ethics review

Approved WMO Date:	19-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-003539-12-NL
CCMO	NL63741.018.17