A PIVOTAL, OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF BIVV009 IN PATIENTS WITH PRIMARY COLD AGGLUTININ DISEASE WHO HAVE A RECENT HISTORY OF BLOOD TRANSFUSION

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Part APrimary Objective:• The primary objective of Part A is to determine whether BIVV009 administration results in a >= 2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to >= 12 g/dL and obviates the need for blood transfusion...

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

Summary

ID

NL-OMON50716

Source
ToetsingOnline

Brief title
Cardinal

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, Open-Label, Primary Cold Agglutinin Disease

Outcome measures

Primary outcome

The primary efficacy endpoint is the responder rate as defined in Table 2.

Secondary outcome

• Mean change from baseline in bilirubin (excluding patients with Gilbert*s Syndrome) at the treatment assessment endpoint (mean of values at Week 23, 25, and 26)

• Mean change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale scores at the treatment assessment endpoint

• Mean change from baseline in lactate dehydrogenase (LDH) at the treatment assessment endpoint

• Number of transfusions and number of units after the first 5 weeks of study drug administration

• Mean change from baseline in Hgb at the treatment assessment endpoint

Exploratory efficacy endpoints:

• Time to first transfusion after the first 5 weeks of study drug administration

• Mean change from baseline in QOL, as assessed by the change in the five level

EuroQol - five dimensions questionnaire (EQ-5D-5L) scores at the treatment assessment endpoint

• Mean change from baseline in QOL, as assessed by the change in the 12-item short form survey (SF-12®) at the end of treatment assessment endpoint

• Incidence of solicited symptomatic anemia at EOT

• Proportion of patients with Hgb level of >= 12 g/dL at the treatment assessment endpoint

• Incidence of thromboembolic events after the first 5 weeks of study drug administration

• Median time to normalization of bilirubin

• Median time to normalization of LDH

• Median time to normalization of haptoglobin

• Median time to obtain Hgb level of >= 12 g/dL

• Proportion of patients normalizing haptoglobin at the treatment assessment endpoint

• Proportion of patients normalizing bilirubin at the treatment assessment endpoint

• Proportion of patients normalizing LDH at the treatment assessment endpoint

• Patient*s Global Impression of Change (PGIC) to assess patient*s perception of changes in CAgD disease burden at EOT

• Incidence of disabling circulatory symptoms at EOT

Part B

The following parameters of disease activity will be assessed:

• Hemoglobin

• Bilirubin (total)

• QOL assessments (FACIT-Fatigue, EQ-5D-5L, SF-12, PGIC and PGIS)

• LDH

• Transfusion requirements

• Haptoglobin

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 to prevent 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

Part A
Primary Objective:
• The primary objective of Part A is to determine whether BIVV009

administration results in a >= 2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to >= 12 g/dL and obviates the need for blood transfusion during treatment in patients with primary CAgD who have a recent history of transfusion
Secondary Objectives:
Efficacy:
• 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 quality of life (QOL) in patients with primary CAgD
Safety:
• To evaluate the overall safety and tolerability of BIVV009 in patients with primary CAgD
Exploratory:
• To assess the effect of BIVV009 on specific complications of CAgD (acrocyanosis, Raynaud*s syndrome, hemoglobinuria, and thromboembolism)
• To evaluate the effect of BIVV009 on certain disease-related biomarkers in patients with primary CAgD
• To evaluate the pharmacokinetics of BIVV009
Part B
Primary Objective:
• The primary objective of Part B is to evaluate the long-term safety and tolerability of BIVV009 in patients with primary CAgD.
Secondary Objective:
• 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 open-label, single-arm study is designed to evaluate the efficacy, safety, and tolerability of BIVV009 in patients with the complement-mediated disorder primary CAgD who have a recent history of transfusion.
During the 6-week Screening/Observation Period, prospective patients will have a detailed medical history documented (including transfusion history of >= 6 months), physical evaluations for screening, and blood samples collected for characterization of CAgD biomarkers, including Hgb levels on 3 occasions approximately every 2 weeks.
Patients may receive a transfusion(s) during the Screening/Observation Period prior to the first study drug infusion if medically indicated per the Investigator*s discretion. However, the baseline visit (and first infusion of study drug) must occur at least 7 days following the transfusion.
Part A
The study will enroll 20 primary CAgD patients who have a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Eligible patients will receive an intravenous (IV) infusion of BIVV009 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 1 week prior to the next scheduled dose in order to receive an additional loading dose. 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 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 in Part A 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 either of the following criteria:

• Hgb level is >= 12 g/dL at treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26), or

• Hgb increased >= 2 g/dL from baseline (defined as the last Hgb value before administration of the first dose of study drug) at treatment assessment endpoint

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 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 6-month treatment period, patients will continue to receive BIVV009 dosing during Part B, the long-term safety and durability of response extension phase. Part B will run for approximately one year following LPO under Part A.

Patients will be dosed with BIVV009 every 2 weeks, as in Part A. 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, and additional safety and efficacy measures. PK, PD and antidrug antibodies (ADA) samples will be collected 6 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.
The overall risk/benefit balance for participants in Study BIVV009-03 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

1.Adult males and females >= 18 years of age at Screening
2.Body weight of >= 39 kg at screening
3.Confirmed diagnosis of primary CAgD 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 degrees Celsius,
e.IgG DAT <= 1+, and
f.No overt malignant disease

4.History of at least one documented blood transfusion within 6 months of enrollment
5.Hemoglobin level <= 10.0 g/dL
6.Bilirubin level above the normal reference range
7.Ferritin level within the normal reference ranges unless outside normal range and deemed not clinically significant by the Investigator (or designee)
8.Presence of one or more of the following CAgD-related signs or symptoms within 3 months of Screening:
a.Symptomatic anemia defined as:
i.Fatigue,
ii.Weakness,
iii.Shortness of breath,
iv.Palpitations, fast heart beat
v.Light headedness and/or
vi.Chest pain
b.Acrocyanosis
c.Raynaud's syndrome
d.Hemoglobinuria
e.Disabling circulatory symptoms, and/or
f.Major adverse vascular event (including thrombosis)
9.Bone marrow biopsy within 6 months of Screening with no overt evidence of lymphoproliferative disease or other hematological malignancy. An additional bone marrow biopsy will be required if the prior bone marrow is deemed unsuitable for analysis by the Sponsor.
10.Vaccinations against encapsulated bacterial pathogens (Neisseria meningitis, Meningitis B, Haemophilus
influenzae, and Streptococcus pneumoniae) within 5 years of enrollment or as specified in Appendix B.
11. Adequate IV access
12. If female, must be post-menopausal, surgically sterile, or be established on (>= 3 months prior to Screening)
and agree to continue to use the same highly effective methods of birth control throughout the study and for 6
weeks following administration of the last dose of study drug
13. Males must be surgically sterile for at least 90 days or when sexually active with female partners of childbearing
potential will agree to use highly effective contraception from Day 0 until 6 weeks days following
administration of the last dose of study drug.
14. Able to comprehend and give informed consent
15. Able to comply with the requirements of the study and to complete the full sequence of protocol-related procedures.

Exclusion criteria

1.Cold agglutinin syndrome secondary to infection, rheumatologic

disease, or active hematologic malignancy
2.Clinically relevant infection of any kind within the month preceding enrollment (eg, active hepatitis C, pneumonia)
3.Clinical diagnosis of systemic lupus erythematosus (SLE); or other autoimmune disorders with anti-nuclear antibodies at Screening.
4.Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody) prior to or at Screening
5.Positive human immunodeficiency virus (HIV) antibody at Screening
6.Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrollment
7.Concurrent treatment with corticosteroids other than a stable daily dose equivalent to <= 10 mg/day prednisone for previous 3 months
8.Erythropoietin deficiency. Concurrent treatment with erythropoietin is permitted if the patient has been on a stable dose for the previous 3 months.
9.Concurrent usage of iron supplementation unless the patient has been on a stable dose for at least 4 weeks.
10.Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the patient or compromise the quality of the data derived from his/her participation in this study (as determined by the Investigator [or designee]) at Screening
11.Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days or 5 half lives, whichever is greater, prior to treatment start
12.Females who are pregnant, lactating, or, if having reproductive potential, are considered potentially unreliable with respect to contraceptive practice

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-12-2017
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:	12-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2020
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	EUCTR2017-003538-10-NL
CCMO	NL63736.018.17