A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Emicizumab in Patients with Mild or Moderate Hemophilia A without FVIII Inhibitors

Published: 15-11-2019
Last updated: 10-04-2024

This study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild (FVIII level between > 5% and < 40%) or moderate hemophilia A (FVIII level between >= 1% and

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON48013

Source
ToetsingOnline

Brief title
BO41423, HAVEN 6

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Bleeding disorder, Hemophilia A

Research involving

Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman-La Roche

Intervention

Keyword: Emicizumab prophylaxis, Hemophilia A, Hemophilia A without FVIII inhibitors

Outcome measures

Primary outcome

Safety endpoints:

• Incidence and severity of adverse events, with severity determined according

to WHO Toxicity Grading Scale

• Incidence of thromboembolic events

• Incidence of thrombotic microangiopathy (TMA)

• Change from baseline in physical examination findings

• Change from baseline in and vital signs

• Change from baseline in ECG parameters

• Incidence of laboratory abnormalities

• Incidence and severity of injection-site reactions

• Incidence of adverse events leading to drug discontinuation

• Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

• Incidence and significance of anti-emicizumab antibodies

• Incidence of de novo development of FVIII inhibitors

Efficacy endpoints:

• Number of treated bleeds over time (i.e., bleed rate)

Secondary outcome

Secondary Efficacy endpoints:

• Number of all bleeds (i.e., those treated and untreated with FVIII) over time

• Number of joint bleeds over time

• Number of target joint bleeds over time (target joints are defined as joints

with

• 3 bleeds occurring in the same joint during the last 24 weeks)

• Number of spontaneous bleeds over time (spontaneous bleed rate)

• Joint health, as assessed through use of the Hemophilia Joint Health Score

(HJHS) at specified timepoints

• Health-related quality of life (HRQoL), as assessed through use of the

Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire

over time

• Preference for emicizumab compared with previous FVIII regimen, as assessed

through use of the Emicizumab Preference Survey (EmiPref) at Week 17

• Effect of emicizumab prophylaxis treatment on physical activity compared with

physical activity at baseline

PK endpoint:

• Plasma concentration of emicizumab at specified timepoints

Immunogenicity endpoints:

• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs

during the study

• Number and proportion of patients who develop anti-FVIII inhibitors (titer >=

0.6 BU/mL) at specified timepoints

Biomarkers:

The exploratory biomarker objective for this study is to investigate the effect of emicizumab on PD parameters, including but not limited to thrombin generation, FVIII activity, FVIII protein, D-dimer, and prothrombin fragment 1+2 (PF1+2) at regular intervals throughout the study and at times of treated bleeds. Changes over time in biomarkers related to bone and joint health may also be explored.

Health Status Utility Endpoint:

• Change from baseline in EuroQol 5-Dimension 5-level Questionnaire (EQ-5D index utility and visual analog scale (VAS) scores at specified timepoints

Study description

Background summary

Hemophilia A is bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity.

Whereas patients with mild and moderate disease generally report a significantly lower number of joint bleeds compared with those with severe hemophilia, there are patients with non-severe disease who present with recurrent articular bleeds.

In patients who experience multiple spontaneous bleeds (regardless of their specific FVIII level), a prophylactic approach is beneficial as it will prevent the occurrence of bleeds and their consequences. Given the clinically meaningful efficacy of emicizumab in the prevention of bleeds and the major benefit it offers over available agents, emicizumab is considered an appropriate option in the medical armamentarium for individuals with non-severe hemophilia A who require prophylaxis.

This study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild or moderate hemophilia without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment.

Study objective

This study will evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients of all ages with mild (FVIII level between > 5% and < 40%) or moderate hemophilia A (FVIII level between >= 1% and <= 5%) without inhibitors against FVIII whose bleeding phenotype warrants prophylactic treatment. Specific objectives and corresponding endpoints for the study are outlined in section 2 of the protocol. Summarized:

• The safety objective for this study is to evaluate the safety profile of emicizumab in patients with non-severe hemophilia A without inhibitors.
• The primary efficacy objective for this study is to evaluate the efficacy of emicizumab.
• The PK objective for this study is to characterize the emicizumab PK profile.
• The immunogenicity objective for this study is to evaluate the immune response to Emicizumab.
• The exploratory biomarker objective for this study is to investigate the effect of emicizumab on PD parameters.
• The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with emicizumab.

Study design

Study BO41423 is a multicenter, open-label, single-arm study designed to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in patients with mild or moderate hemophilia A without inhibitors against FVIII.

Intervention

Emicizumab (also known as ACE910, RO5534262, and HEMLIBRA) is a recombinant, humanized, bispecific, immunoglobulin G4 monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII.

Four loading doses of emicizumab 3 mg/kg will be administered subcutaneously QW for 4 weeks followed by patient preference of one of the following maintenance regimens:

• 1.5 mg/kg QW;
• 3 mg/kg Q2W;
• 6 mg/kg Q4W.

The three maintenance dose regimens have shown equivalent average steady-state exposure, and demonstrated consistent efficacy and safety, and are approved in several countries for the treatment of Hemophilia A with or without FVIII inhibitors. As patients with mild or moderate Hemophilia A have residual FVIII levels of >= 1%, it is of interest to collect safety data over a longer time period.
Therefore, in this study, the observation time to primary analyses was extended to approximately 52 weeks compared with prior Phase III studies investigating emicizumab.

Study burden and risks

The general burden on the patient consists, among other things, of blood sampling (each visit), and the administration of the study drug (depending on the treatment regimen chosen, varying from every week to every 4 weeks) that may lead to various adverse events.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Signed Informed Consent Form (signed by patient*s legally authorized representative for patients who have not attained the age of majority)
• Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
• Willingness and ability to comply with schedules visits, treatment plans, laboratory tests and other study procedures
• Diagnosis of mild (FVIII level between >5% and <40%) or moderate (FVIII level between >= 1% and <= 5%) congenital Hemophilia A without FVIII inhibitors
• Weight >= 3 kg
• Need for prophylaxis based on investigator assessment
• A negative test for inhibitor (i.e., < 0.6 BU/mL) within 8 weeks prior to enrollment
• No documented inhibitor (i.e., < 0.6 BU/mL), FVIII half-life < 6 hours, or FVIII recovery < 66% in the last 5 years
• Patients who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by a detection of an inhibitor, FVIII half-life <6 hours or FVIII recovery <66% since completing ITI.
• Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks prior to enrollment

• Adequate hematologic function, defined as platelet count >= 100,000 cells/µL and hemoglobin >= 8 g/dL (4.97 mmol/L) at the time of screening
• Adequate hepatic function defined as total bilirubin <= 1.5 X age-adapted upper limit of normal (ULN) (excluding Gilbert syndrome) and both AST and ALT <= 3 x age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
• Adequate renal function, defined as serum creatinine <= 2.5x age-adapted ULN and creatinine clearance >= 30 mL/min by Cockroft-Gault formula
• For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined in section 4.1.1 of the Clinical Protocol

Exclusion criteria

• Inherited or acquired bleeding disorder other than mild (FVIII level between > 5% and < 40%) or moderate (FVIII level between >= 1% and <= 5%) congenital hemophilia A
• History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator*s judgment
• Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
• Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
• History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
• Planned surgery during the emicizumab loading dose phase (surgeries in patients on emicizumab from Week 5 onwards are allowed)
• Known HIV infection with CD4 counts < 200 cells/µL
• Concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would in the opinion of the investigator, pose an additional unacceptable risk in administering study drug to the patient
• Receipt of any of the following
o An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration with the exception of prior emicizumab prophylaxis (prior investigational or commercial emicizumab use is not an exclusion criterion)
o A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
o Any other investigational drug currently being administered or planned to be administered
• Inability to comply with the study protocol in the opinion of the investigator
• Pregnant or breastfeeding, or intending to become pregnant during the study

(women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2020
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hemlibra
Generic name:	Emicizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	07-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

(Assen)

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	EUCTR2019-002179-32-NL
CCMO	NL71583.056.19
Other	nog onbekend