Protocol EFC16293: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc von Willebrand Factor XTEN Fusion Protein (rFVIIIFc VWF XTEN; BIVV001) in Previously Treated Patients *12 Years of Age With Severe Hemophilia A.

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This study is being conducted to determine the safety and efficacy of the study drug BIVV001 when used as a once-a-week prophylaxis treatment or as an on-demand (as-needed) treatment for bleeding in patients 12 years and older with severe hemophilia…

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

Summary

ID

NL-OMON54973

Source
ToetsingOnline

Brief title
XTEND-1

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym
Severe Hemophilia A; severe bleeders disease A

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Industry;Bioverativ - Sanofi

Intervention

Keyword: - In Previously Treated Patients 12 Years of Age., - Intravenous Recombinant Coagulation Factor, - New Generation Coagulation Factor VIII with a prolonged half life - called BIVV001. administered as weekly profylaxis or as 'on demand' treatment., - Severe Hemophilia A.

Outcome measures

Primary outcome

Primary Efficacy Endpoint;

- Annualized bleeding rate (ABR) in Arm A

Safety Endpoints:

-The occurrence of adverse events (AEs) and serious adverse events (SAEs)

- The occurrence of clinically significant changes from baseline in physical

examination, vital signs, and laboratory tests

- Development of inhibitors (neutralizing antibodies directed against factor

VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay

- The occurrence of embolic and thrombotic events

Pharmacokinetic Endpoint:

- PK parameters including, but not limited to, maximum activity (Cmax), elimination half-life (t1/2), total clearance (CL), total clearance at steady state (CLss), accumulation index (AI), area under the activity time curve (AUC), volume of distribution at steady state (Vss), mean residence time (MRT), incremental recovery (IR), trough activity (Ctrough), time above predefined FVIII activity levels

Secondary outcome

Secondary Efficacy Endpoints: * Intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A who participated in Study 242HA201/OBS16221, an observational study (key secondary endpoint) * ABR by type and location for prophylaxis treatment per study arm * ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm * Intra-patient comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B * Percentage of participants who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A * Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen * Percentage of bleeding episodes treated with a single injection of BIVV001 per study arm and treatment regimen * Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale per study arm and treatment regimen * Physician*s global assessment (PGA) of participant*s response to BIVV001

treatment based on a 4-point response scale per study arm and treatment regimen * Total annualized BIVV001 consumption per participant per study arm and treatment regimen * Annualized Joint Bleeding Rate (AJBR) per study arm and treatment regimen * Target joint resolution at Week 52, based on ISTH criteria in Arm A * Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS) in Arm A * Changes in PROMIS-SF Physical Function (*18 years old) measures from Baseline to Week 52 in Arm A * Changes in Haem-A-QoL (* 17 years old) total score and physical health score measures from baseline to Week 52 in Arm A * Investigators* or Surgeons* assessment of participant*s hemostatic response to BIVV001 treatment on the ISTH 4-point response for surgical procedures scale * Number of injections and dose to maintain hemostasis during perioperative period for major surgery * Total BIVV001 consumption during perioperative period for major surgery * Number and type of blood component transfusions used during perioperative period for major surgery * Estimated blood loss during perioperative period for major surgery

Study description

Background summary

BIVV001 is a recombinant fusion protein consisting of single-chain FVIII, the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D*D3 domain of von Willebrand factor (VWF), and 2 XTEN linkers. It is believed that the plasma t* of FVIII is prolonged by its interaction with VWF. BIVV001 is the first rFVIII engineered to be independent of VWF, theoretically extending its t*. Nonclinical studies of BIVV001 have demonstrated that its t* is significantly prolonged compared with current FVIII products.

Brief summary of clinical data of BIVV001
The BIVV001 clinical development program includes a completed Phase 1/2a study (242HA101) and a clinically completed Phase 1 study (242HA102) evaluating the safety, tolerability, and PK of BIVV001 administered as single and repeat IV doses, respectively. In Study 242HA101, 15 participants received a single dose of BIVV001. In Study 242HA102, 24 participants had received at least 1 dose of BIVV001.

Study 242HA101 Safety results: No inhibitor development to FVIII was detected and there were no reports of serious hypersensitivity or anaphylaxis. Overall, single dose BIVV001 was well tolerated and no safety concerns were identified. Regarding SAE's/ SUSAR's refer to Investigator's Brochure.

PK results: The geometric mean of half-life was 42.5 hours for BIVV001 compared with 13.2 hours for Advate based on FVIII activity measured by the one-stage aPTT clotting assay [geometric means ration (GMR)=3.2 (95% CI: 2.8, 3.8); p<0.001] in the high-dose (65 IU/kg) cohort.

Study 242HA102 Safety results: No inhibitor development to FVIII was detected and there were no reports of serious hypersensitivity or anaphylaxis.

Pk results: A very detailed description of the chemistry, pharmacology, and safety of BIVV001 is provided in the BIVV001 Investigator*s Brochure. As this was a Phase 1 study the results are too many to summarize here.

Study objective

This study is being conducted to determine the safety and efficacy of the study drug BIVV001 when used as a once-a-week prophylaxis treatment or as an on-demand (as-needed) treatment for bleeding in patients 12 years and older with severe hemophilia A who have previously been treated with a FVIII product or cryoprecipitate for at least 150 days. The study will also assess how the study drug is processed in the body (eg, distributed, transformed, and removed); this is called pharmacokinetics (PK).

Primary Efficacy Objective
- To evaluate the efficacy of BIVV001 as a prophylaxis treatment

Secondary Efficacy Objectives
- To evaluate the efficacy of BIVV001 as a prophylaxis treatment
- To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes
- To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes
- To evaluate the effect of BIVV001 prophylaxis on joint health outcomes
- To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes
- To evaluate the efficacy of BIVV001 for perioperative management

Safety Objective:
- To evaluate the safety and tolerability of BIVV001 treatment

Pharmacokinetic Objective:
To assess the PK of BIVV001 based on the onestage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays

Study design

This is a multinational, multicenter, open-label Phase 3 study of the safety, efficacy, and PK of IV BIVV001 in previously treated patients (PTPs) *12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). The study is comprised of 2 Arms: Arm A and Arm B.
Participants currently on a prophylaxis treatment regimen with FVIII will enter Arm A and receive BIVV001 at a dose of 50 IU/kg IV QW. Participants currently on an on-demand treatment regimen will enter Arm B for 26 weeks of on-demand treatment of bleeding episodes with BIVV001 at a dose of 50 IU/kg IV on demand, then switch to receive BIVV001 at a dose of 50 IU/kg IV QW on a prophylaxis treatment regimen for 26 weeks.

Following a washout period (at least 4 to 5 days, depending on current therapy), all participants (except those in the sequential PK subgroup of Arm A) will undergo abbreviated PK sampling after the first dose of BIVV001 (Baseline). Sixteen participants at selected sites will participate in the sequential PK subgroup of Arm A and will undergo more extensive PK sampling at Baseline and again at Week 26.

Participants from any arm who undergo major surgery during the study will be included in the surgery subset. A minimum of 10 major surgeries in at least 5 patients will be targeted to assess control and prevention of bleeding in the surgical setting. The definition of major surgery is included in Section 10.6.

Intervention

Number of participants:

Approximately 150 participants will be enrolled to collect sufficient data to assess the safety, efficacy, and PK of IV BIVV001 in this population. Approximately 124 participants will be in Arm A, of which at least 75 participants will have had at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline. Sixteen participants from Part A will be included in the sequential PK subgroup. Approximately 26 participants will be in Arm B. For the surgery subset, a minimum of 10 major surgeries in at least 5 participants will be targeted to assess control and prevention of bleeding in the surgical setting.

Intervention groups and duration:

Participants in Arm A will receive a QW prophylactic dose of BIVV001 for 52 weeks. Participants in Arm B will receive BIVV001 on demand for 26 weeks followed by a switch to QW prophylaxis for another 26 weeks.

Study intervention(s):

Investigational medicinal product(s) * Formulation: Recombinant coagulation factor VIII Fc-von Willebrand Factor XTEN Fusion Protein. * Route(s) of administration: Intravenous * Dose regimen: The dose regimen of Arm A consists of a prophylactic dose regimen of 50 IU/kg IV QW for 52 weeks. The dose regimen of Arm B is comprised of 2 parts: an on-demand dose regimen of 50 IU/kg IV for 26 weeks, and a prophylactic regimen of 50 IU/kg IV QW for 26 weeks.

Study burden and risks

Benefits

BIVV001 is designed to be a next-generation extended half-life blood clotting FVIII engineered to be independent of VWF. Next-generation extended half-life FVIII products that prevent and control bleeding episodes for longer periods of time potentially reduce the burden of frequent IV administration and in turn, may improve adherence and outcomes, including quality of life for individuals with hemophilia A. In addition to the patient burden that results from frequent administration it is well established that the currently accepted FVIII activity trough level (1 to 3 %) is not adequate to protect patients from all bleeds and the resulting morbidity associated with such bleeding episodes. Joint bleeds still occur at these levels, leaving patients susceptible to long-term morbidity. The ability to increase patient protection by achieving higher sustained levels of factor activity remains a critical need for patients and follows recommendations from the World Federation of Hemophilia. BIVV001 has the potential to achieve and maintain higher factor activity levels than currently available therapies, with less frequent administration, which would represent a major advance in hemophilia management.

Risks
There is a long history of therapeutic use of rFVIII products in the treatment of hemophilia A, with a well-recognized and understood safety profile. Patients treated with other rFVIII products have reported adverse reactions that include hypersensitivity, anaphylaxis, and development of inhibitors. Based on the currently available non-clinical data (in vivo and in vitro) it is expected that BIVV001 will have a safety profile similar to other rFVIII products. The safety and tolerability of BIVV001 in previously treated adults with severe hemophilia A was evaluated in a completed single dose Phase 1/2a study (Study 242HA101) and also in an ongoing repeat dose Phase 1 study (Study 242HA102). Single dose BIVV001 was well tolerated and no safety concerns were identified.

As of 07 February 2019, the data cut off of the interim analysis for Study 242HA102, repeat doses of BIVV001 were well tolerated and no inhibitors were detected.

Conclusion
Overall, the clinical development program for BIVV001 is supported by the available nonclinical and clinical data as well as the potential benefits associated with development of a rFVIII product with an extended half-life that offers increased protection in the treatment of individuals with hemophilia A. More detailed information may be found in the Investigator*s Brochure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
Age
01. Participant must be equal to or greater than 12 years of age inclusive, at the time of signing the informed consent.
02. Severe hemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII activity as documented either by central laboratory testing at Screening or in historical medical records from a clinical laboratory demonstrating <1% FVIII coagulant activity (FVIII:C) or a documented genotype
known to produce severe hemophilia A.
03. Previous treatment for hemophilia A (prophylaxis or on demand) with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs.
04. Current regimen includes one of the following: * Prophylactic treatment regimen with a marketed FVIII product or prophylactic emicizumab therapy for at least 6 months during the previous 12 months. Appropriate washout time needs to be taken into account. * On-demand regimen with a marketed FVIII product with a history of at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment. - On-demand participant is accepting to move to a prophylaxis treatment regimen after 26-week on-demand period.
05. Platelet count *100,000 cells/*L at Screening.
06. A participant known to be human immunodeficiency virus (HIV) antibody positive, either previously documented or identified from screening assessments, must have the following results prior to enrollment.
a. CD4 lymphocyte count >200 cells/mm³
b. Viral load of <400 copies/mL
Documented results of CD4 lymphocyte count and viral load will be accepted if samples were collected within 26 weeks prior to Screening or if samples were collected during Screening and evaluated by the central laboratory.
Participants who have previously tested negative for HIV must have a repeat test by the central laboratory during Screening
07. Willingness and ability of the participant or surrogate (a caregiver or a family member *18 years of age) to complete training in the use of the study electronic Patient Diary (ePD) and to use the ePD throughout the study.
Sex
08. Male or Female
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. a) Male participants - No contraceptive measures required for this study. b) Female participants - A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: - Is not a woman of childbearing potential (WOCBP), as defined in Section 10.4

or - Is a WOCBP and using an acceptable contraceptive method as described Section 10.4 during the intervention period (at a minimum until Safety Follow-up Call or Visit). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention. and - A WOCBP must have a negative highly sensitive pregnancy test before the first dose of study intervention as described in Section 10.2.
A serum pregnancy test should be performed at screening. For all other time points, serum or urine pregnancy testing may be performed at the discretion of the Investigator.
Additional requirements for pregnancy testing during and after study intervention are located in Section 10.2
The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
Informed Consent
09. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. [In countries where legal age of majority is above
18 years, a specific ICF must also be signed by the participant*s legally authorized representative.]
10. Ability of the participant or his or her legally authorized representative (eg., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent or assent (as applicable) and authorization to use protected health information in accordance with national and local participant privacy regulations.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
Medical conditions

01. Any concurrent clinically significant liver disease that, in the opinion of the Investigator, would make the participant unsuitable for enrollment. This may include, but is not limited to cirrhosis, portal hypertension, and acute hepatitis.
02. Serious active bacterial or viral infection (other than chronic hepatitis or HIV) present within 30 days of Screening.
03. Other known coagulation disorder(s) in addition to hemophilia A.
04. History of hypersensitivity or anaphylaxis associated with any FVIII product
05. History of a positive inhibitor test defined as *0.6 BU/mL, or any value greater than or equal to the lower sensitivity cut-off for laboratories with cut-offs for inhibitor detection between 0.7 and 1.0 BU/mL, or clinical signs

or symptoms of decreased response to FVIII administrations. Family history of inhibitors will not exclude the participant.
06. Positive inhibitor result, defined as *0.6 BU/mL at Screening.
07. Abnormal renal function, defined as serum creatinine >2.0 mg/dL taken at Screening.
08. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN) taken at Screening.
09. Serum total bilirubin >3 x ULN, taken at Screening.

Prior/concomitant therapy

10. Vaccination within 30 days of Screening
11. Treatment with acetylsalicylic acid (ASA) within 2 weeks prior to screening
12. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) above the maximum dose specified in the regional prescribing information within 2 weeks prior to Screening.
13. Systemic treatment within 12 weeks prior to Screening with chemotherapy and/or other immunosuppressive drugs (except for the treatment of hepatitis C virus [HCV] or HIV). Use of corticosteroids is allowed, except for systemic corticosteroid treatment given daily or on alternate days for >14 days. Local, topical, and/or inhaled steroid use is permitted.

Prior/concurrent clinical study experience

14. Emicizumab use within the 20 weeks prior to Screening
15. Previous enrolment in this study; participants who fail Screening may re-screen
6. Treatment with an investigational product within 30 days or 5.5 half-lives prior to Screening, whichever is longer. For investigational products with a pharmacodynamic effect that persists longer than the half-life, the maximal pharmacodynamic effect must return to baseline prior to Screening.

Other exclusions

17. Major surgery within 8 weeks prior to Screening. Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (eg, laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).
18. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized
19. Any country-related specific regulation that would prevent the participant from entering the study * see Appendix 10 (Section 10.10) (country specific requirements)
20. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants

potentially at risk of noncompliance to study procedures
21. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6)
22. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals
23. Any specific situation during study implementation/course that may raise ethical considerations
24. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study

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):	07-09-2020
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BIVV001 - Recombinant human coagulation FVIII Fc □ von Willebrand factor □ XTEN fusion protein
Generic name:	BIVV001

Ethics review

Approved WMO Date:	25-11-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-04-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-08-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-10-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2019-002023-15-NL
CCMO	NL71848.100.19
Other	U1111-1223-4867 (WHO) / 17464 (IND) / NCT04161495