ISRCTN11492145 https://doi.org/10.1186/ISRCTN11492145

Octapharma’s FVIII concentrates in previously untreated and minimally treated haemophilia A patients

Submission date
16/04/2019

Recruitment status
Recruiting

Registration date
29/05/2019

Overall study status
Ongoing

Last Edited
06/06/2024

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Haemophilia A results from an abnormality in the blood that affects its ability to clot. Blood clotting is the process that controls bleeding. It changes blood from a liquid to a solid form. This is a complex process involving many different blood chemicals or proteins, known as clotting factors. When certain clotting factors are missing or don't work properly, clotting of blood doesn't occur as it should.
In people with severe haemophilia A, an important clotting factor called factor VIII (FVIII) is missing or doesn't work the way it should. This causes people with haemophilia A to bleed for a longer time than people whose blood FVIII levels are normal. The preferred treatment for haemophilia A is a FVIII replacement therapy. Octapharma’s FVIII concentrates have been tested in clinical trials and registered for treatment of haemophilia A; however, as haemophilia A is a rare disease, only small numbers of patients have been treated. For previously untreated patients (PUPs), who are typically young children, and for minimally treated patients (MTPs), who have been exposed to only minimal FVIII dosages, more information is needed on treatment effectiveness and safety, specifically related to inhibitor development. Also, for PUPs, treatment algorithms are not standardized, e.g. with respect to utilisation, dosage, frequency or optimal start age of FVIII. The aim of this study is thus to evaluate product utilisation, effectiveness and safety, including inhibitor development, in severe haemophilia A PUPs and MTPs, who have been prescribed Octapharma’s FVIII concentrates.

Who can participate?
Patients with severe haemophilia A who have been prescribed Octapharma’s FVIII concentrate and who have never received a FVIII product before or have received a FVIII product for fewer than 5 days

What does the study involve?
This is an observational study, where treatment of severe haemophilia A patients is documented. For the FVIII concentrates evaluated, effectiveness is measured as the number of breakthrough bleeds during prophylactic treatment, and further FVIII utilization pattern (on-demand, surgery). Safety is assessed as the occurrence of hypersensitivity reactions and FVIII

inhibitor development after treatment with any of Octapharma's FVIII concentrates. In addition to the documentation of the individual treatment, there are sub-studies related to blood samples (taken during routine visits). The sub-study samples are analysed in central laboratories. The sub-studies provide additional information on the background of inhibitor development as well as on inhibitor eradication.

Each patient is observed for 100 exposure days to the chosen FVIII product. Frequency of treatment may vary from every other day to every two weeks. In patients developing a FVIII inhibitor, and where an immune tolerance induction is initiated, the maximum observational time is 3 years.

What are the possible benefits and risks of participating?
Participation in this study will help to obtain additional information on the effectiveness and safety of the prescribed FVIII product, and the dosage regimens used, and may contribute towards the development of effective treatment strategies for future haemophilia A patients. Because this is a non-interventional study assessing a routine treatment, no additional risks are expected from being in the study. The FVIII product has been licensed. The study doctor will inform participants about possible risks, side effects and discomfort as part of the routine treatment information.

Where is the study run from?
Prof. Johannes Oldenburg, University Hospital Bonn (Germany)

When is the study starting and how long is it expected to run for?
January 2017 to June 2030

Who is funding the study?
Octapharma AG (Switzerland)

Who is the main contact?
Mrs Martina Jansen
martina.jansen@octapharma.com

Contact information

Type(s)
Public

Contact name
Mrs Martina Jansen

Contact details
Oberlaaerstrasse 235
Vienna
Austria
1100
+43 664 9227867
martina.jansen@octapharma.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT03695978

Secondary identifying numbers
GENA-25

Study information

Scientific Title
Practical utilization of Octapharma FVIII concentrates in previously untreated and minimally treated haemophilia A patients entering routine clinical treatment (with Nuwiq, Octanate or Wilate)

Acronym
Protect-NOW

Study objectives
The purpose of this study is to evaluate FVIII utilisation, effectiveness and safety in previously untreated (PUPs) and minimally treated (MTPs) severe haemophilia A patients prescribed with Octapharma's FVIII products in a real-world setting, to understand real life treatment patterns and facilitate life-cycle benefit-risk profiling.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/09/2017, Rheinische Friedrich-Wilhelms-University Ethics Committee (Biomedical Center, Sigmund-Freud-Str. 25, 53127 Bonn, Germany; Tel: +49 (0)228 287 51 282; Email: ethik@uni-bonn.de), ref: 207/17

Study design
Post-marketing prospective and retrospective non-interventional study (NIS)

Primary study design
Observational

Secondary study design
Epidemiological study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Haemophilia A

Interventions
This is an observational study, where treatment of severe haemophilia A patients is documented. For the FVIII concentrates evaluated, effectiveness will be measured as the number of breakthrough bleeds during prophylactic treatment, and further FVIII utilization pattern (on-demand, surgery). Safety will be assessed as the occurrence of hypersensitivity reactions and FVIII inhibitor development post-treatment with any of Octapharma's FVIII concentrates.

In addition to the documentation of the individual treatment, patients' parents are offered to join sub-studies, which are related to blood samples (taken during routine visits). The sub-study samples are analysed in central laboratories. The sub-studies will evaluate parameters to provide additional information on the background of inhibitor development as well as on inhibitor eradication.

Each patient will be observed for 100 exposure days to the chosen FVIII product. Frequency of treatment may vary from every other day to every two weeks. In patients developing a FVIII inhibitor, and an immune tolerance induction is initiated, the maximum observational time will be 3 years.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Nuwiq, octanate, wilate

Primary outcome measure
Products' effectiveness in the treatment of bleeding episodes (BEs) and as prophylactic treatment:
1. Prophylactic treatment effectiveness is measured using the annualized rate of all bleeding episodes (BEs) (Annualized Bleeding Rate, ABR), including and differentiated into all spontaneous, all traumatic and all joint BEs. Patients' parents have a diary, where all BEs need to be documented. These BEs are reviewed by the treating physician (together with the parents), and transcribed into the eCRF.
The observational period is 100 exposure days (EDs) for patients treated prophylactically or on demand.
For patients undergoing immune tolerance therapy after inhibitor to FVIII development may be up to 3 years.
2. The effectiveness of treatment at the end of a BE will be assessed by the patient's parent or legal guardian as applicable, or by the treating physician in case of treatment at the treatment centre, using a scale including the four items 'excellent,' 'good,' moderate,' and 'none':
Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion

Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 – 12 hours after an infusion requiring up to 2 infusions for complete resolution
Moderate: Probable or slight beneficial effect within approximately 12 hours after the first infusion requiring more than two infusions for complete resolution
None: No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution
The observational period is 100 exposure days (EDs) for patients treated prophylactically or on demand.
The observational period for patients undergoing immune tolerance therapy after inhibitor to FVIII development may be up to 3 years.

Secondary outcome measures

1. Products' utilization patterns, including dosage and frequency of application. To assess usage of Octapharma's FVIII concentrates in the treatment of PUPs and MTPs with severe haemophilia A in real life, individual patient information on concentrate selection, dosage, duration and treatment frequency, as well as changes over time of Octapharma's FVIII concentrates will be collected and analysed. Patients' observational period will vary – depending from the treatment intensity: patients will stay for 100 EDs, or for a max. of 3 years, if they developed an inhibitor to FVIII and initiated immune tolerance induction therapy.
2. Products' effectiveness in surgical prophylaxis. The overall assessment of the effectiveness of any surgical prophylaxis treatment during the patient's participation in the project, done by the treating physicians will be assessed using a scale including the four items 'excellent,' 'good,' moderate,' and 'none':
Excellent: No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with Octapharma's FVIII concentrate, as anticipated for the type of procedure.
Good: No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with Octapharma's FVIII concentrates or additional infusions, not originally anticipated for the type of procedure.
Moderate: Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with Octapharma's FVIII concentrates or additional infusions, not originally anticipated for the type of procedure.
None: Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate FVIII concentrate.

The optional sub-studies will aim at assessing factors potentially associated with inhibitor development and inhibitor eradication in patients with severe haemophilia A and will include:
1. Anti-FVIII non-neutralising antibodies measured using modified Bethesda test, please see epitope mapping below for the timepoints
2. F8 gene analysis, measured using standard gene mutation analysis of blood sample taken once during the entire study
3. Epitope mapping performed using a microsphere-based bead assay on a Luminex machine at the following timepoints:
3.1. A baseline sample should be taken prior to first treatment with any FVIII concentrate (background)
3.2. Optional sample after 10 ED, likely without inhibitor
3.3. Optional for patients not developing inhibitors: a sample after the first 50-100 ED (also used for non-neutralising antibody detection)
3.4. Optional for patients developing inhibitors: a sample after inhibitor development (preferably within the 1-10 ED after inhibitor development)

3.5. ITI samples every 3 months during the course of ITI
3.6. For non-neutralising antibody detection, if after successful inhibitor eradiation inhibitor titer is <0.6 BU/ml
4. Product-specific batch selection for Wilate and Octanate (only applicable for patients with inhibitor who undergo immune tolerance induction). If treating physician and patients' parents agree to start ITI with a selected batch of the plasma-derived product, the Oxford method is used. Timepoints are not defined: the test is done when a specific batch is needed after inhibitor development. During the ITI, a new batch might be required, when the earlier batch was completely used. The same Oxford method applies.

Overall study start date
01/01/2017

Completion date
30/06/2030

Eligibility

Key inclusion criteria
1. Male and female patients of any age and ethnicity
2. Severe haemophilia A (FVIII:C<1%)
3. Decision to prescribe Octapharma's FVIII concentrate before enrolment into the study
4. Either no previous treatment with FVIII concentrates or other blood products containing FVIII (PUPs) OR less than 5 Exposure Days (EDs) to FVIII concentrates or other blood products containing FVIII (MTPs)
5. Voluntarily given, fully informed written and signed consent obtained before any study-related data documentation is conducted (obtained from the patient's parent/legal guardian)

Participant type(s)
Patient

Age group
All

Sex
Both

Target number of participants
200

Key exclusion criteria
1. Diagnosis with a coagulation disorder other than haemophilia A
2. Concomitant treatment with any systemic immunosuppressive drug
3. Participation in an interventional clinical trial during the time period evaluated
4. Participation in another non-interventional study of Octapharma

Date of first enrolment
11/02/2018

Date of final enrolment

30/06/2030

Locations

Countries of recruitment
Belarus

Belgium

Canada

Croatia

France

Germany

Hungary

Italy

Lithuania

Mexico

Spain

United Kingdom

United States of America

Study participating centre
Prof. Johannes Oldenburg, University Hospital Bonn
Venusberg-Campus 1
Bonn
Germany
53127

Sponsor information

Organisation
Octapharma AG

Sponsor details
Seidenstrasse 2
Lachen

Switzerland
8853
+41 (0)554512166
larisa.belyanskaya@octapharma.com

Sponsor type
Industry

ROR
https://ror.org/002k5fe57

Funder(s)

Funder type
Industry

Funder Name
Octapharma AG (Switzerland)

Results and Publications

Publication and dissemination plan
Not available yet

Intention to publish date
30/12/2030

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available except to the authorities, if requested.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.3.0	23/01/2019	14/06/2019	No	Yes
Participant information sheet	version 2.0	21/09/2020	17/08/2021	No	Yes
Results article		10/05/2023	15/05/2023	Yes	No