PARENT INFORMATION AND INFORMED CONSENT FORM

for

Non-Interventional Study GENA-25

PRactical utilization of **O**ctapharma FVIII Concentrates in Previously Untreated and Minimally **T**reated Haemophilia A Patients **E**ntering Routine **C**linical **T**reatment (with **N**uwiq, **O**ctanate or **W**ilate)
A Real-World Efficacy and Safety Observational Study

Sponsor:	**Octapharma AG** Lachen, Switzerland
Principal Investigator:	**<name>** <institution> <address>

Dear Parent(s),

Your child's doctor has prescribed treatment with one of Octapharma's factor VIII (FVIII) products (i.e., *Octanate*®, *Wilate*®, or *Nuwiq*®) to your child. The purpose of treatment with a FVIII product is to control and prevent bleedings that may occur as a result of your child's haemophilia.

We now invite your child to take part in a non-interventional study. A study is a way of gathering information on a treatment and answering questions about something that is not well enough understood. In a non-interventional study, a medicine is used in accordance with the terms of the marketing authorization of that product. Thus, the selection of a particular therapy or medicine is clearly separated from the decision to include a patient in the study. Therefore, participation in this non-interventional study will have no influence on the treatment your child will be receiving. Your child's doctor will, however, record your child's treatment data in standardised forms so that the data can later be analysed by an independent statistics institute.

Please take the time to read this **Information Sheet** on this carefully and feel free to ask questions about anything you don't understand before deciding whether or not you wish your child to participate.

Taking part in this study is voluntary. Even if you now choose to have your child in the study, you have the right to stop at any time. If you decide not to have your child participate or to leave the study early, your child's usual health care will not be affected.

1 Why is my child asked to participate in this study?

Your child is being asked to consider participating in this study because it has haemophilia A. 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 8' or '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.

2 Why is this study being done?

You and your study doctor have decided that your child will undergo treatment with one of Octapharma's FVIII products. This decision has been made independently of this study. The only difference between routine FVIII treatment and this study is that, in this study, all treatment details will be carefully documented not only in your child's medical records, but also in standardised forms for later statistical analysis.

The data will be analysed to answer the following questions (see **Section 7.1**):

- How well does the FVIII product treat or prevent bleedings in patients with haemophilia A?
- How well is the product tolerated?
- How effective is the product at controlling blood loss during surgeries?
- What FVIII treatment schedules and dosages are used in clinical practice?

In addition to the data routinely recorded during FVIII treatment, you can also choose to have some additional parameters assessed. These will be analysed to answer the following questions (see **Section 7.2**):

- What is the role of non-inhibiting anti-FVIII antibodies in the treatment of haemophilia A?
- How do anti-FVIII antibodies bind to their binding sites ('epitopes') on the FVIII molecule?
- Do certain genetic mutations have an effect on the risk of bleeding or inhibitor development?

3 Does my child have to undergo FVIII therapy?

Your doctor has recommended FVIII replacement therapy for your child because this is the preferred treatment for haemophilia A. Injecting FVIII makes the clotting factor immediately available in

the bloodstream, and the body can activate it to continue the clotting cascade and control the bleeding risk.

People with haemophilia A are treated either with FVIII products that are made from **donated human blood** (such as *Octanate*® or *Wilate*®) or with **biotechnologically produced FVIII products** that are produced from cell lines (such as *Nuwiq*®).

Also, there are two basic options for FVIII treatment, i.e., treatment may be given at the time a bleed occurs (known as **'on-demand therapy'**), or it may be given regularly to prevent bleeds from occurring (known as **'prophylactic therapy'**).

Your child's doctor will select the treatment regimen s/he considers the best option for your child.

4 How many patients will participate in this study?

Overall, 140 patients with haemophilia A from approximately 50 treatment centres worldwide will be enrolled into this study.

5 What are the main criteria for participating in this study?

This study is open to participation to patients with severe haemophilia A who have:

- never before received a FVIII product
- received a FVIII product on fewer than 5 days, with the first administration having taken place after 1 January 2015.

There are also a number of reasons that prevent your child from participating in this study, namely the presence of a blood clotting disorder other than haemophilia A, the presence of a FVIII inhibitor, the treatment with drugs that act on the immune system, or participation in an interventional clinical study.

6 How long will the study last?

The overall study duration will be about 5 years (2017 to 2022). To obtain solid results, each patient should be in the study for 100 'exposure days' (i.e., days on which the FVIII product is administered) or a maximum time of 3 years.

7 What will be done in this clinical study?

Before any study-specific documentation will take place, your doctor will discuss the study with you, and you will be asked to read this **Information Sheet** and sign the **Informed Consent Form** at the end of this document.

7.1 Routine FVIII treatment

First visit

During the first visit, your doctor will explain all treatment details to you and discuss what data will be obtained in case you decide that your child may participate in the study. He will answer any of your questions. The **demographic and baseline data**, such as your child's body weight, height, age, medical and bleeding history, laboratory parameters, and any additional diseases, will be documented.

You will be handed out a **Treatment Diary** in which to record any observations in connection with your child's health. Your doctor will explain to you how to fill in the diary and emphasize the importance of carefully documenting all treatment details, bleeding episodes, side effects of treatment, illnesses, or hospitalizations as well as any additional medications your child may be taking throughout the study.

If bleedings occur, you will also be asked to assess the effectiveness of FVIII treatment in the Treatment Diary once the bleeding has stopped. Please bring your child's Treatment Diary along to each study visit so that your doctor can monitor the effectiveness of treatment, adapt recommendations and record and transcribe the data.

Follow-up visits

During routine standard visits, the frequency of which will be discussed between you and your doctor, your doctor will document results of examinations and laboratory tests. Especially during the start of a regular treatment with a FVIII concentrate, the FVIII level and the presence of inhibitors are routinely checked more frequently.

During these visits, your doctor will also review the Treatment Diary to find out whether the prescribed treatment regimen works well for your child. You will also be asked about any side effects that may have occurred since your last visit.

In addition to the regular visits described above, you and your child may need to visit the treatment centre in case of severe bleedings, emergencies, surgeries, or if you suspect that your child may have developed a FVIII inhibitor.

7.2 Additional assessments

In addition to the assessments routinely performed almost worldwide during FVIII treatment start and further follow up, you may decide to have some additional not yet golden standard parameters recorded. These parameters could, in the future, help to further individualise haemophilia A treatment, predict a patient's risk of developing inhibitors, or even prevent the formation of inhibitors:

Measurement of non-inhibiting anti-FVIII antibodies

In this study, it is intended to check for the presence of non-inhibiting anti-FVIII antibodies. In contrast to inhibiting antibodies, the role of non-inhibiting antibodies is currently not clear. If you agree to this

type of testing, *no* additional blood samples will have to be taken, because these antibodies can be tested by using the samples taken for routine inhibitor testing as described above.

Epitope mapping

'Epitopes' are small regions on the FVIII molecule that are recognised by anti-FVIII antibodies and that these antibodies bind to. Through this binding mechanism, the antibodies attack the FVIII molecule so that it cannot fulfil its desired function of setting off a chain of reactions that ultimately form a blood clot. Characterization of these regions may improve the understanding of the mechanisms of inhibitor activity and may aid in the development of new therapies. If you agree to this type of testing, a small aliquot of a routinely taken blood sample will be provided to a central laboratory in Germany at predefined times during the study. This is a part of a sample taken for treatment purposes - no extra blood will be taken.

F8 genotyping

'Genotyping' has become golden standard in analysing haemophilia A patients for many years, already. It is the process of identifying specific genetic changes responsible for a person's disorder. Within this study, a blood sample can be provided to a central laboratory in Germany, if agreed upon. Gene mutation analysis will be used to test for any mutations in your child's FVIII gene. For example, certain F8 genotypes have been linked with an increased risk of severe bleeding or inhibitor development.

8 What are the possible benefits of the study?

Your child's 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.

The study may also allow to assess the effect of non-inhibiting anti-FVIII antibodies, FVIII epitopes, and certain genetic characteristics affecting the bleeding risk and treatment outcome. In this way, your child may contribute towards the development of effective treatment strategies for future haemophilia A patients.

9 What are the possible risks and discomforts when taking part in this study?

Because this is a non-interventional study assessing a routine treatment, no additional risks are expected from your child of being in the study. The FVIII product your child will receive for treatment has been licensed in your country. The study doctor will inform you about possible risks, side effects and discomfort as part of the routine treatment information.

10 What are the costs of your participation in this study?

All costs related to this study are covered under your medical care plan. The haemophilia treatment centre will provide you with the FVIII product and additional items needed to infuse the product, such as syringes or needles. You will not be paid for your child being in this study.

11 Confidentiality
Information and Declaration of Consent for Parents on Data Protection during a Non-Interventional Study in Accordance with the General Data Protection Regulation, EU 2016/679

During the non-interventional study, medical findings and personal information are collected from your child and entered in your child`s personal file or stored electronically at the trial site. Data important for non-interventional study are additionally stored in pseudonymised form (see below), evaluated and, if necessary, passed on.

Pseudonymised means that no names or initials are used, but only a number and/or letter code, possibly indicating the month and year of birth.

The following information details storage and use of your child`s personal data. You will also be informed of your rights regarding your child`s personal data.

a) Legal Basis

In handling the data collected in the course of the non-interventional study, the provisions of the General Data Protection Regulation EU 2016/679 will be observed. All persons who have access to this data as a result of their professional activities are bound by data secrecy, without prejudice to other legal obligations.

According to GDPR EU 2016/679, "personal data" means all information relating to an identified or identifiable natural person (study participant). “Indirect personal data" is data whose personal reference is such that the identity of the study participants cannot be determined by legally permissible means.

b) How Will the Data Collected During this Non-Interventional Study be Used?Unless otherwise provided by law, only investigators and their staff have access to the confidential data in which your child is named ("personal" data”).

Where necessary, European supervisory authorities or the non-interventional study sponsor may also inspect this data to verify the accuracy of the records. These persons are subject to a statutory duty of confidentiality.

The data will only be passed on at home and abroad for statistical purposes in pseudonymised or non-personalised ("anonymised") form, i.e. they will not be named. Where necessary, this information may be passed on to the client of the clinical trial or his representative for scientific evaluation, to an approval authority within the framework of product approval and to the responsible higher federal authority in the event of undesirable events and from the latter to a European database.

Your child will not be named in any publication of the data of this non-interventional study.

If you withdraw your consent for your child to participate in the non-interventional study and thus terminate his/her participation prematurely, no further data will be collected about your child. However, due to legal documentation requirements (Medicines or Medical Devices Act), your child’s personal data can still be inspected by authorised persons who are bound to secrecy for a legally stipulated period (usually 15 years) for testing purposes.

c) Personal Rights and their Exercise

You are entitled to the rights listed below. To assist you in exercising these rights, please contact the persons listed below.

You have the right to receive information about your child`s personal data and to have access to it. If the data concerning your child is incorrect, you can have it corrected. In addition, you have the right to restrict the extent to which your child`s data is used, in deviation from the extent defined in this consent. In addition, you may at any time, without affecting your child`s medical treatment, request the deletion of the data concerning your child, unless its storage is prescribed by other legal regulations. Personal data will be deleted as soon as they are no longer required for the purposes stated herein.

You have the right to receive the personal data concerning your child in a structured and standard format and to have your child`s data transmitted to third parties by the persons responsible without further impediment. Furthermore, you have the possibility to file a complaint with the responsible supervisory authority against the storage, processing and the related processes at any time.

If the persons responsible process the personal data for purposes other than those stated herein, the purpose and all other relevant information will be made available to you in advance.

If you have any questions about data protection, your/ your child`s rights and how to exercise them, please do not hesitate to contact following persons:

Data Protection Officer of Principal Investigator

Contact information:

Data Protection Officer of Sponsor of the Study

Contact information:

Octapharma AG, 8853 Lachen, Switzerland

Corporate Data Protection Officer

Email: dataprivacy@octapharma.com

Data Protection Officer of contract research organization

Contact information:

Global Privacy and Data Protection Officer

Syneos Health

3201 Beechleaf Court

Suite 600

Raleigh, NC 27604-1547

USAEmail: Data.Privacy@syneoshealth.com

12 Who do I call if I have questions?

For further questions in connection with this non-interventional study, your investigator and his staff will be at your disposal. Questions concerning your rights as parents of a child participating in this non-interventional study will also be answered. As soon as general results of this non-interventional study are available, you can also be informed if you wish. If you have additional questions regarding this non-interventional study, please contact the study doctor:

Study doctor

Name:	
Address:	
Phone:	
Fax:	

Thank you for reading this Information Sheet.

If you decide to have your child take part in this study,
please enter your name on the attached
Informed Consent Form and sign and date it.

Informed Consent Form

1. **I agree that my child`s personal data (age, health information, laboratory values, information in the questionnaires) collected in the context of and for the purpose of this non-interventional study will be processed and transmitted indirectly (pseudonymised) to the sponsor or his representative (contract research organisation) for the purpose of scientific evaluation.**
2. **I understand that the data collected by the investigator may be inspected to verify the accuracy of the data recording by the competent authorities and the sponsor or his representative.**
3. **I am aware that I can request information about my child`s personal data from those responsible at any time.**
4. **I am aware that I can have personal information corrected or rectified without giving reasons.**
5. **I am also aware that I can revoke my consent to the use of my child`s data at any time without giving reasons and without adverse consequences for my child`s medical treatment, whereby a revocation generally causes the inadmissibility of further use of the data, unless other legal regulations or predominant legitimate interests continue to permit the use of the data.**
6. **I have the right to receive my child`s personal data in a structured, common and machine-readable format and I have the right to have this data transmitted to another person in charge without further interference.**
7. **I herewith agree that my child's data shall be stored for at least ten years after termination or discontinuation of the project. Thereafter, the personal data will be deleted, unless required otherwise by law, statutes, or contractual provisions.**
8. **I am aware that I have the right to lodge a complaint with the competent supervisory authority at any time.**
9. **I have received a copy of this parent information and consent form. The original remains with the investigator.**

Please mark appropriate check box(es) below.

Based on the information available to me,

☐ **Yes**, I agree to have my child take part in the project.

☐ **Yes**, I agree to have my child take part in "Additional Assessments" of this project.

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Name of my child

Signatures

Patient's parent(s) or legal guardian:

I agree to have my child take part in this study as stated above.

Print name	Signature	Date

Patient's parent(s) or legal guardian:

I agree to have my child take part in this study as stated above.

Print name	Signature	Date

Treating Physician:

Print name	Signature	Date