CLINICAL STUDY PROTOCOL

STUDY TITLE

Phase 1/2 study to assess the safety and pharmacokinetics of subcutaneous injection of OCTA101 in previously treated adult patients with severe hemophilia A

Study Code: SubQ8-01

Investigational Product:	OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Indication:	Severe hemophilia A
Study Design:	Prospective, open-label study, dose-finding
Sponsor:	**Octapharma AG** Seidenstrasse 2 8853 Lachen Switzerland
Study Number:	SubQ8-01
EudraCT:	2018-002776-40
Development Phase:	Phase 1/2
Planned Clinical Start:	Quarter 2 2019
Planned Clinical End:	Quarter 3 2022
Date of Protocol:	30-Jul-2021
Version:	9.0 Revision of Protocol Version 8.0, dated 03-Mar-2021
Co-ordinating Investigator:	[redacted]

STUDY OUTLINE

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

Title of Study: Phase 1/2 study to assess the safety and pharmacokinetics of subcutaneous injection of OCTA101 in previously treated adult patients with severe hemophilia A.

Indication: Severe hemophilia A

Number of Study Centers: 1 center

Objectives:

Primary Objective:

The primary objective is to assess the safety of various doses of OCTA101 after subcutaneous (sc) injection.

Secondary Objectives:

The secondary objectives of this study are to assess

- the pharmacokinetics of FVIII:C after single sc injection of OCTA101
- the dose proportionality of FVIII:C after sc injections of different doses of OCTA101
- the bioavailability of sc OCTA101 compared to iv injection of Nuwiq
- the pharmacokinetics of OCTA12 (recombinant human von Willebrand Factor fragment dimer) after single injection of OCTA101
- plasma trough and peak levels of FVIII:C after daily injections of OCTA101
- plasma trough and peak levels of OCTA12 after daily injections of OCTA101
- the efficacy of sc injections of OCTA101 in preventing bleeding episodes.

Name of Sponsor/Company: Octapharma AG	
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Study Design:

SubQ8-01 is a first-in-human, prospective, open-label Phase 1/2 study of OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer), which consists of an eluate of an already authorized human recombinant coagulation factor FVIII product (Nuwiq®) along with OCTA12 (at a molar ratio of 1:6, with regards to FVIII binding sites in OCTA12), an investigational human recombinant VWF fragment dimer, which is expected to increase the bioavailability of FVIII on subcutaneous (sc) dosing. The trial was to be carried out in adult patients with severe hemophilia A according to a staged integrated design with five planned consecutive cohorts. No patient can receive treatment in more than 1 cohort. One part of the study was to be a single ascending dose study in 4 cohorts (50, 100, 200 and 400 IU/kg). The decision of going to the next higher dose was to be taken after each cohort by an external independent Data Monitoring Committee (DMC) after review of safety and tolerability data, FVIII:C plasma levels, and PK characteristics of FVIII:C and OCTA12. Any safety-relevant signals were also forwarded to the DMC for their review as they occurred. The reason(s) for not progressing to a higher dose level, e.g. dose-limiting toxicities (DLTs), were to be documented if such a decision was reached.

Pre-defined DLTs for this study are:

1. Severe allergic reactions at least possibly related to study drug.
2. Severe vital organ toxicity at least possibly related to study drug that does not resolve to at least mild severity within 48 to 72 hours.
3. Any treatment-emergent severe toxicity at least possibly related to study drug other than the toxicities referenced in 2) that does not decrease to mild or resolve within 7 days.

Based on the results from Cohorts 1 and 2, the sponsor and DMC decided that escalation to higher doses should not take place and that further characterization of 50 IU/kg and lower doses was warranted. Therefore, Cohort 3 received 50 IU/kg administered into the abdomen, Cohort 4 was to receive 50 IU/kg administered into the thigh (this was not proceeded with, as described below), and Cohort 5 investigated dose linearity at a lower dose range than initially planned (20, 40 and 60 IU/kg instead of 50, 100 and 200 IU/kg).

Patients in Cohort 3 also received a single iv dose of 50 IU/kg Nuwiq in order to compare the bioavailability of sc OCTA101 with those of Nuwiq (the FVIII part of OCTA101) injected intravenously (iv). The treatment sequence was Nuwiq followed by OCTA101. Dose

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

proportionality of OCTA101 was evaluated after single sc administration of three different doses (20 IU/kg, 40 IU/kg and 60 IU/kg) in 4 additional patients (Cohort 5).

A PK assessment was performed in patients from Cohorts 1 and 2 who completed their 3-month daily injection period.

Following completion of the PK assessments in Cohort 3 and 1-month into OCTA101 daily prophylaxis in this cohort, the study was put on hold due to inhibitor development in a second patient (in Cohort 2).

Due to the study hold, patients in Cohort 3 were switched to prophylaxis with Nuwiq after having received 1-month of OCTA101 daily prophylaxis. Patients in Cohort 3 completed the study when their overall time on daily prophylaxis (OCTA101 + Nuwiq) reached 3 months. By the time of preparation of protocol version 8.0, Cohorts 1, 2 (with the exception of 1 patient with FVIII inhibitors who entered ITI treatment with Nuwiq), 3, and 5 were completed.

With the agreement of the DMC, it was decided to proceed with the study, introducing the following changes to the study design. Cohort 4 was cancelled and Cohort 5 was cut from 8 patients to 4.

A new cohort (Cohort 6) was initiated for 16 evaluable patients. In this cohort, patients have an initial 4 to 6-week run-in treatment period with Nuwiq iv prophylaxis followed by 12.5 IU/kg OCTA101 sc daily prophylaxis for >3 up to 6-7 months. With DMC agreement, the patients will then proceed to 25 IU/kg OCTA101 sc daily prophylaxis for 6-7 months. Based on the results of both dosing phases, a 40 IU/kg OCTA101 will be considered. Cohort 6 is planned to proceed as follows:

- Following completion of the run-in period with Nuwiq iv prophylaxis, 3 patients started daily dosing with 12.5 IU/kg OCTA101 sc.
- After 3 months of treatment with OCTA101, the patients had their 3-month follow-up visit. During the 2 to 3 weeks waiting for all relevant results, especially FVIII inhibitor testing results, these patients continued on daily dosing with 12.5 IU/kg OCTA101 sc.
- DMC agreed that further patients can start their daily prophylaxis with OCTA101, up to 16 patients proceeded with 12.5 IU/kg OCTA101. After further 3 months, following DMC data review, the first 3 patients of this cohort were planned to start on daily dosing with 25 IU/kg OCTA101 sc for 6-7 months. The remaining patients were planned to follow after a further 3 months, after DMC data review.
- Patients reporting two spontaneous bleeding episodes will be switched to the next higher dose level after having completed at least 3 months with 12.5 IU/kg OCTA101 daily treatment: they will start daily dosing with 25 IU/kg OCTA101 sc.

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

- Depending on the results of the 12.5 IU/kg and 25 IU/kg OCTA101 treatment phases, the initiation of a 40 IU/kg OCTA101 phase will be considered together with the DMC.
- Bleeding episodes will be controlled with the use of Nuwiq during the entire duration of treatment in Cohort 6.

The cohorts are summarized as follows:

- **Cohort 1:** 50 IU/kg OCTA101 (n=4): Single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing.

  DMC assessment after last patient of Cohort 1. If ok, proceed with Cohort 2, and also with daily prophylactic dosing (approximately 40-60 IU/kg) for 3 months (initially with Nuwiq but then with OCTA101 if advised by the DMC). Patients from Cohort 2 and 3 may also start their daily prophylactic dosing for 3 months immediately after collection of the last PK sample.
- **Cohort 2:** 100 IU/kg OCTA101 (n=4): Single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing.

  DMC assessment after last patient of Cohort 2. If ok, proceed with Cohort 3.
- **Cohort 1 and 2:** PK assessment after 3-month daily dosing (n=8): single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 120 hours after dosing for FVIII and up to 21 days for OCTA12.
- **Cohort 3:** 50 IU/kg OCTA101 (n=8): Two-period investigation of a single iv dose of 50 IU/kg Nuwiq profiled for up to 72 hours after dosing followed by sc dose of 50 IU/kg OCTA101 administered into the abdomen profiled up to 72 hours. Treatments were to be administered in fixed sequence, with Nuwiq first.

  DMC assessment after last patient of Cohort 3. If ok, proceed with Cohort 4 and 5.
- **Cohort 4:** 50 IU/kg OCTA101 (n=4): Cancelled.
- **Cohort 5:** (n=4) *[8 had been planned]*: Three-period investigation of single sc doses of 20, 40, and 60 IU/kg OCTA101 profiled up to 72 hours after dosing. Treatments were to be administered in fixed dose-ascending sequence.
- **Cohort 6** (n≥16): Following an initial 4 to 6-week run-in period with Nuwiq iv prophylaxis, >3-6 months daily prophylactic treatment with 12.5 IU/kg OCTA101 sc, then 25 IU/kg OCTA101 sc for a further 6-7 months (exact dosing depends on available vial sizes). In case of two spontaneous bleeding episodes, after having completed at least 3 months with 12.5 IU/kg OCTA101 daily treatment the individual treatment dose will be increased from 12.5 to 25 IU/kg. Site of administration

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

(abdomen or thigh) to be chosen by the patient. A further treatment phase with 40 IU/kg OCTA101 will be discussed with the DMC, once results of earlier dosing phases are available.
The DMC will review and assess the available results approximately every 3 months.

By DMC-recommendation, patients enrolled in Cohorts 1, 2, and 3 proceeded to 3-month prophylactic treatment part of the study and received daily dosing using one injection (approximately 40-60 IU/kg; dose chosen to allow administration by single injection; it was permitted to daily alternate the vial size, e.g. 3000 IU on one day 1, 5000 IU on day 2, 3000 IU on day 3, 5000 IU on day 4 etc.) of OCTA101 for 3 months (home treatment). Patients from Cohort 1 received prophylactic Nuwiq (home treatment) until the DMC had confirmed that OCTA101 can be used as daily prophylaxis. Bleeding events during the study were treated with Nuwiq. Throughout this part of the study, FVIII inhibitors, plasma concentrations of FVIII:C, and OCTA12 were measured repeatedly.

Independent expert evaluation by the DMC has steered study progress for the stepwise dosage increments by cohort and the progression of patients from the first three cohorts to 3-month daily dosing. In addition, the DMC has advised on changes of the proposed dosage for the assessment of bioavailability (Cohort 3) and dose-proportionality (Cohort 5) and changes in the schedule of PK blood sampling and/or the duration of profiling without substantially increasing the total amount of blood to be sampled. Based on the observation of a second patient with inhibitors in Cohort 2, the DMC recommended placing the study on hold. The DMC recommended restarting the study with the implementation of Amendment 3, which cancelled Cohort 4, cut Cohort 5 to 4 patients instead of the planned 8, and introduced Cohort 6 investigating OCTA101 sc prophylaxis over 6-7 months of treatment per dose level following a run-in period with Nuwiq iv prophylaxis. The DMC will continue to be involved in the further conduct of the study.

This study started in Q2 2019 and is planned to be completed by Q3 2022.

Number of Patients: N = 36 evaluable in total (16 evaluable patients in Cohort 6)

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

Patient Selection Criteria:

Inclusion Criteria:

Patients who meet all of the following criteria are eligible for the study:

1. Severe hemophilia A (<1% FVIII:C) as documented in medical records
2. Males ≥18 years of age
3. Subjects who have had ≥150 exposure days (EDs) with a FVIII product
4. Written informed consent for study participation obtained before undergoing any study specific procedures

Exclusion Criteria:

Patients who meet any of the following criteria are *not* eligible for the study:

1. Previous participation in this trial
2. Use of an Investigational Medicinal Product within 30 days prior to the first OCTA101 injection
3. History of FVIII inhibitors titer ≥0.6 BU/mL defined by medical records
4. Inhibitors to FVIII (≥0.6 BU/mL) at screening measured by Nijmegen modified Bethesda method at central laboratory
5. Human immunodeficiency virus (HIV) positive subjects with a $CD4^+$ count <200/mL
6. Clinically significant anemia at screening (hemoglobin <8 g/dL)
7. Presence of any significant comorbidity (at the discretion of the investigator) that might confound the interpretation of the study data and/or that might put the patient at undue risk by participating in the trial
8. Any coagulation disorder other than hemophilia A
9. AST or ALT levels >3 times the upper limit of normal
10. Creatinine >120 µmol/L
11. Platelet count <100,000 µL
12. BMI ≥30 kg/m²
13. For Cohort 6, patients with a positive LumiTope test at screening will be excluded.

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

Test Product, Dose, and Mode of Administration:

OCTA101 is composed of rFVIII (derived from commercial Nuwiq) and the recombinant VWF fragment dimer OCTA12, at a molar ratio of 1:6 (with regards to FVIII binding sites in OCTA12).

OCTA101 will be injected sc at doses as described above. OCTA101 will be provided as lyophilized powder in vials containing 500 IU, 750 IU, 1000 IU and 2000 IU (plus 3000 IU and 5000 IU in cohorts 1-5). Each vial needs to be reconstituted with 1.0 mL of Water for Injection. The site of sc injection (abdomen or thigh) must be documented.

In all cases, the minimum number of injections required to provide the required dose must be administered.

Nuwiq is a human cell line derived recombinant FVIII concentrate for iv use. Vials contain 500°IU, 1000 IU, 2000 IU or 3000 IU of freeze-dried FVIII concentrate, each to be reconstituted in 2.5 mL water for injections. Nuwiq should be injected iv by bolus injection at a maximum rate of 4 mL/min.

Duration of Treatment (as planned):

Cohort 1: Single injection of OCTA101 50 IU/kg sc with 72 hours of observation.

Cohort 2: Single injection of OCTA101 100 IU/kg sc with 96 hours of observation.

Cohort 1 and 2: At the end of the daily injection period and after a wash-out of at least 72 hours after the last OCTA101 injection, or any other FVIII injection, the PK of FVIII:C and OCTA12 was to be assessed with an OCTA101 dose of 50 IU/kg. FVIII:C and OCTA12 levels were to be measured up to 120 hours; thereafter, additional samples will be taken to measure OCTA12 at the following time points: 7, 14 and 21 days. After the 120 hour time point patients could use Nuwiq for prophylaxis or treatment of bleeding episodes until the last sampling time point.

Cohort 3: Single injection of Nuwiq 50 IU/kg iv with 72 hours of observation, followed by single injection of OCTA101 50 IU/kg sc into the abdomen with 72 hours of observation.

Cohorts 1, 2 and 3: Daily injections of OCTA101 approximately 40-60 IU/kg sc for 3 months.

Cohort 4: (Cancelled) Single injection of OCTA101 50 IU/kg sc into the thigh with 72 hours of observation.

Cohort 5: Single injection of OCTA101 20 IU/kg sc with 72 hours of observation, followed by single dose of OCTA101 40 IU/kg sc with 72 hours of observation, followed by single

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

dose of OCTA101 60 IU/kg sc with 72 hours of observation (4 patients into the abdomen, 4 patients into the thigh).

Cohort 6: Following an initial 4 to 6-week run-in period with Nuwiq iv prophylaxis, >3-6 months daily prophylactic treatment with 12.5 IU/kg OCTA101 sc, then 25 IU/kg OCTA101 sc for a further 6-7 months. In case of two spontaneous bleeding episodes, after having completed at least 3 months with 12.5 IU/kg OCTA101 daily treatment the individual treatment dose will be increased from 12.5 to 25 IU/kg. Depending on the results of the first two treatment phases, a further treatment phase with 40 IU/kg OCTA101 will be considered.

Reference Therapy, Dose, Mode of Administration:

None.

Study Outcome Parameters (Primary and Secondary Endpoints):

Safety Parameters:

Primary:

- Adverse events
- DLTs
- Thromboembolic events
- Local injection site reactions
- Inhibitor formation to FVIII

Secondary:

- Antibody formation to OCTA12
- LumiTope assay results
- OCTA12 plasma levels during daily dosing
- Routine lab tests compared to baseline
- Vital signs compared to baseline
- Physical examination results compared to baseline

Efficacy Parameters:

Secondary:

- PK parameters of FVIII:C (AUC, C_{max}, T_{max}, IVR, $t_{1/2}$, MRT, CL [iv dosing only], Vd [iv dosing only])
- PK parameters of OCTA12, same parameters as above

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

- Total annualized bleeding rate during daily sc treatment with OCTA101
- Spontaneous annualized bleeding rate during daily sc treatment with OCTA101
- Total annualized treated bleeding rate during daily sc treatment with OCTA101
- Spontaneous annualized treated bleeding rate during daily sc treatment with OCTA101
- Traumatic annualized treated bleeding rate during daily sc treatment with OCTA101
- Annualized joint bleeding rate during daily sc treatment with OCTA101
- FVIII:C trough and peak plasma levels during daily dosing
- Score (4-point rating scale) to assess efficacy of treatment of bleeding episodes with Nuwiq

Study Procedures:

Screening Visit – all patients

The following assessments will be performed:

• Informed consent
• Eligibility criteria
• Demographics: age, ethnic origin
• Blood type (ABO)
• $CD4^+$ count
• Medical history
• Previous and concomitant medication, including FVIII treatment details in previous 6 months and bleeding frequency
• Body weight
• Height
• Physical examination
• Hemophilia Joint Health Score (HJHS)
• Target joint(s) (defined as three or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding screening visit)
• Vital signs: systolic and diastolic blood pressure, body temperature, pulse (before blood sample collection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay)
• Routine safety lab: Hematology: red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count. Clinical chemistry: total bilirubin, ALT, AST, urea, serum creatinine, lactate dehydrogenase
• Start of monitoring of adverse events (AEs)

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

• Cohort 6: LumiTope assay (negative test result required)

Any bleeding episodes occurring between the Screening Visit and the first exposure with OCTA101 (or Nuwiq in Cohort 6 patients) should be treated with the patient's previously used FVIII concentrate.

Following screening, eligible patients will receive a patient diary after the first treatment. The investigator will explain to the patient how to fill in the diary and will emphasize the importance of carefully documenting all treatment details, adverse events, and concomitant medications.
PK assessments should be performed after a washout period of at least 72 h, if possible, from the last FVIII injection. Patients must not be experiencing any bleeding.

Cohort 1 patients – single dose PK, OCTA101 50 IU/kg sc
The following assessments will be performed:
• Body weight (before injection)
• Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h and 72 h after injection)
• Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h and 72 h after injection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
• Blood sample for anti-OCTA12 measurement (before injection)
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after injection).
• Blood samples for measurement of OCTA12, as above for FVIII:C
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Cohort 2 patients – single dose PK, OCTA101 100 IU/kg sc
The following assessments will be performed:
• Body weight (before injection)
• Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection)
• Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
• Blood sample for anti-OCTA12 measurement (before injection)

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection).
• Blood samples for measurement of OCTA12, as above for FVIII:C
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Cohort 3 patients – single dose PK, Nuwiq 50 IU/kg iv, followed by single PK OCTA101 50 IU/kg sc into the abdomen
The following assessments will be performed:
Nuwiq injection (iv)
• Body weight (before injection)
• Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h, and 72 h after injection)
• Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h, and 72 h after injection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, and 72 h after injection
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period
OCTA101 injection (sc into the abdomen)
• Blood sample for anti-OCTA12 measurement (before injection)
• Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after injection)
• Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after injection)
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) before injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection
• Blood samples for measurement of OCTA12, as above for FVIII:C
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Cohort 4 patients – single dose PK, OCTA101 50 IU/kg sc into the thigh
Cancelled

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

Cohort 5 patients – single dose PK of OCTA101 20 IU/kg, followed by single PK of OCTA101 40 IU/kg sc, followed by single dose PK of OCTA101 60 IU/kg sc
The following assessments will be performed:
<u>OCTA101 injection 20 IU/kg into the abdomen (4 patients)</u>
• Body weight (before injection)
• Vital signs (before injection, 8 h, 12 h, 24 h, 48 h and 72 h after the injection)
• Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h and 72 h after the injection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection)
• Blood sample for anti-OCTA12 measurement (before the injection)
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Blood samples for measurement of OCTA12, as above for FVIII:C
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period
<u>OCTA101 injection 40 IU/kg into the abdomen (4 patients)</u>
• Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Blood samples for measurement of OCTA12, as above for FVIII:C
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period
<u>OCTA101 injection 60 IU/kg into the abdomen (4 patients)</u>
• Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay)
4 weeks after injection
• Blood sample for anti-OCTA12 measurement 4 weeks after injection
• Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
• Blood samples for measurement of OCTA12, as above for FVIII:C

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Cohort 1, 2 and 3 patients – daily injections for 3 months, OCTA101 40 - 60 IU/kg sc
Patients entering the 3-month daily prophylactic part will be trained in sc self-administration of study medication. Patients in Cohort 1 will be required to return to the study site for their first daily dose; patients in Cohorts 2 and 3 will still be present at the study site at the time of their first daily dose. The following assessments will be performed:
• Vital signs (before and 3 h and 6 h after the injection at the beginning of the 3-month daily dosing and 0.5, 1, 2, and 3 months thereafter)
• Routine safety lab (before and 3 h and 6 h after the injection at the beginning of the 3-month daily dosing and 0.5, 1, 2, and 3 months thereafter)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection and 0.5, 1, 2 and 3 months thereafter)
• Blood sample for anti-OCTA12 measurement, (before the first injection and 0.5, 1, 2 and 3 months thereafter)
• Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 3 h and 6 h after the injection at the beginning and 0.5, 1, 2, and 3 months thereafter)
• Blood sample for OCTA12 measurement, (before and 3 h and 6 h after the injection at the beginning and 0.5, 1, 2, and 3 months thereafter)
• Physical examination (at End of Study) (Cohort 3 only)
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection, for each injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

PK assessment following 3-month daily prophylaxis in Cohort 1 and 2 patients
Patients completing the 3-month daily prophylactic part will attend the study site. The following assessments will be performed:
• After a wash-out of at least 72 hours after the last OCTA101 injection, or any other FVIII injection, a dose of 50 IU/kg OCTA101 sc will be administered
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before and at 21 days after the injection)
• Blood sample for anti-OCTA12 measurement, (before and at 21 days after the injection)

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

• Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 2°h, 4 h, 8 h, 12 h, 24 h, 48 h, 72 h, 96 h, and 120 h after the injection)
• Blood sample for OCTA12 measurement, (before and, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h, 7 days, 14 days, and 21 days after the injection)
• Physical examination (at End of Study)
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Cohort 6: Following 4 to 6-week run-in with Nuwiq iv prophylaxis, patients are prophylactically treated for 6-7 months with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc daily, again for 6-7 months. Depending on the results, a treatment phase with 40 IU/kg OCTA101 may be added

Patients in Cohort 6 will have their first Nuwiq administered at the study site. After the run-in period, patients will be trained in sc OCTA101 self-administration for subsequent home administration.

The following assessments will be performed:

Start of 4 to 6 week Nuwiq run-in:

• Documentation of bleeding episodes and their treatment throughout the run-in period
• Adverse event monitoring throughout the run-in period
• Documentation of concomitant medication throughout the run-in period

Daily OCTA101 treatment periods:

• Vital signs (before and 8 h after the injection OCTA101 at the beginning of each dosing period and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)
• Routine safety lab (before and 8 h after the OCTA101 injection at the beginning of each dosing period and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each of the 6-7 month OCTA101 daily prophylaxis treatment periods)
• Blood sample for anti-OCTA12 measurement, (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each of the 6-7 month OCTA101 daily prophylaxis treatment periods)

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
Name of Active Ingredient: Coagulation factor VIII	**Date of Final Protocol:** 30-Jul-2021

• Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 8°h after the OCTA101 injection at the beginning of the 6-7 month dosing periods and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)
• Blood sample for OCTA12 measurement, (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each dosing period)
• Physical examination (at End of Study)
• LumiTope assay (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each dosing period)
• Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection, for each injection)
• Documentation of bleeding episodes and their treatment throughout the study period
• Adverse event monitoring throughout the study period
• Documentation of concomitant medication throughout the study period

Unscheduled Visits

In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations due to severe bleeding episodes.

Stopping rules

A single death event (with the exception of death from underlying disease or any other death clearly unrelated to OCTA101) that occurs within 30 days of administration of study drug.

According to the revised stopping rules implemented by Amendment 2, the study was to be put on hold until a further DMC recommendation for further conduct of the study was made, if more than one patient met the following criteria:
• Exhibits a consistently high titer FVIII inhibitor (≥5 BU), as determined by central laboratory tests including a retest as detailed in Section 6.1.9.
or
• Exhibits a low titer FVIII inhibitor (≥0.6 BU and <5 BU), as determined by central laboratory test, including a retest as detailed in Section 6.1.9, and a standard recovery test using intravenous factor VIII shows a recovery below 66%. A formal half-life study with determination of the terminal half-life ($t_{½}$) associated with the recovery study is encouraged with the patient in a non-bleeding state and free of any intercurrent illness.

As a further patient with FVIII inhibitors in Cohort 2 subsequently met these criteria, the study was put on hold and patients stopped OCTA101 treatment. The ongoing patients in

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Cohort 3 were switched to Nuwiq prophylaxis for the remainder of the planned 3-month prophylaxis period.

Once Cohort 6 has been initiated, all patients will immediately stop treatment with OCTA101, if another patient develops a confirmed FVIII inhibitor (≥0.6 BU).

In this case, all FVIII inhibitor negative patients will switch to prophylactic treatment with Nuwiq comparable to the run-in phase, and will come for a final follow-up visit after treatment change. During the final follow-up visit the following should be done:

- Routine safety lab
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay)
- Blood sample for anti-OCTA12 measurement
- Blood sample for OCTA12 measurement
- Physical examination
- LumiTope assay
- Documentation of bleeding episodes and their treatment
- Adverse event monitoring
- Documentation of concomitant medication

Summary of status at the time of finalizing the amended study protocol version 9.0:

At the time of finalizing the amended study protocol version 9.0, the following had been completed:

- Cohort 1: 50 IU/kg: single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing – completed as planned in 4 patients. 3-month OCTA101 daily dosing – completed as planned in 4 patients. PK assessment after 3-month daily dosing – completed as planned in 4 patients.
- Cohort 2: 100 IU/kg: single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing – completed as planned in 4 patients. 3-month OCTA101 daily dosing – completed as planned in 2 patients; 2 patients with inhibitors in Cohort 2 discontinued daily OCTA101 prophylaxis and started ITI treatment with Nuwiq. PK assessment after 3-month daily dosing – completed as planned in 1 patient; not performed in the 2 inhibitor patients switched to ITI treatment and a patient with low levels of FVIII. One patient who developed FVIII inhibitors and started ITI died due to a fatal serious adverse event (retroperitoneal hematoma). The second patient undergoing ITI after FVIII inhibitor development is continuing treatment with Nuwiq.

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Name of Investigational Product: OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)	**Protocol Identification Code:** SubQ8-01
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- Cohort 3: 50 IU/kg (n=8): two-period investigation of a single iv dose of 50 IU/kg Nuwiq profiled for up to 72 hours after dosing followed by sc dose of 50 IU/kg OCTA101 administered into the abdomen profiled up to 72 hours – completed as planned in 8 patients. 3-month OCTA101 daily dosing – due to the study hold, patients in Cohort 3 were switched to prophylaxis with Nuwiq after having received about 1-month of OCTA101 daily prophylaxis; the 8 patients in Cohort 3 completed the study when their overall time on daily prophylaxis (OCTA101 + Nuwiq) reached 3 months.
- Cohort 4: 50 IU/kg (n=4): cancelled.
- Cohort 5 (n=4): three-period investigation of single sc doses of 20, 40, and 60 IU/kg OCTA101 profiled up to 72 hours after dosing with 4-week follow-up visit – completed in 4 patients instead of the originally planned 8 patients.
- Cohort 6 (n≥16): Nineteen patients were screened for Cohort 6 since autumn 2020, of whom two failed inclusion-/exclusion criteria, and two withdrew consent. Ten patients started daily treatment with 12.5 IU/kg OCTA101 after a 4-6 weeks prophylactic treatment run-in phase with Nuwiq, 3 times weekly. Further five patients started the 4-6 weeks run-in phase, but they have not yet started treatment with OCTA101.

  After six month daily treatment with OCTA101 a positive FVIII inhibitor result (0.8°BU/mL) was reported for patient C6-Q1-01-02 on 14-Jul-2021. After consultation and in agreement with the DMC the sponsor decided to put the study on-hold with immediate effect: all patients with OCTA101 treatment were switched back to prophylactic treatment with Nuwiq, 3 times weekly. On 27-Jul-2021 a further low-titer FVIII inhibitor was reported for patient C6-Q1-01-10 (1.6 BU/mL).

  It was decided to stop all further treatment with OCTA101, but to offer all enrolled patients access to Nuwiq prophylactic treatment until they are integrated into the National Health Insurance program for haemophilia A patients, again, but no longer than until the end of September 2021 + 2 weeks time window.

  Patients who developed FVIII inhibitors during treatment within cohort 6 are followed up as originally planned in the study protocol.

Statistical Analysis Plan:

Safety and tolerability data will first be analyzed for each cohort after the first dose(s) and evaluated by an external DMC. Two separate analyses will be performed: the first one will include all available data of enrolled patients in Cohorts 1, 2, 3, and 5 and the second one will include all data of the newly defined Cohort 6. Analyses based on data from repeat dosing

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from Cohort 1, 2, and 3 with OCTA101 for 3 months will be analyzed separately from data related to the first doses. In these analyses, data will be presented by cohort and overall. Analysis based on Cohort 6 data will be presented by period (run-in period with Nuwiq and OCTA101 treatment period) and by planned OCTA101 daily dose.

For each cohort

- Descriptive analysis of demographic and baseline variables.
- Safety analyses

The number and percentage of patients with AEs and the number of AEs will be summarized by primary MedDRA System Organ Class (SOC) and Preferred Term (PT). Separate tables showing all AEs, all serious AEs and all AEs at least possibly related to IMP will be generated. Further a summary of AEs by severity, presenting the most severe event per patient overall and within each SOC and PT will be generated.

For thromboembolic events and local injection site reactions, appropriate clusters of MedDRA terms will be defined and such events will be presented within these clusters, using the summaries detailed above.

The frequencies of local injection reactivity ratings by the investigator and the patient will be summarized over time periods. The frequencies (including percentages) of any inhibitor formation to FVIII and antibody formation to OCTA12 will be presented. Vital sign and safety laboratory parameters will be analyzed using descriptive statistics for measured values and for changes from pre-dose values to each single injection.

- Individual non-compartmental individual PK analyses (NCA) of the time courses of FVIII:C (after administration of OCTA101 and Nuwiq) and OCTA12 (administration of OCTA101) including terminal half-life ($t_{½}$), incremental in-vivo recovery (IVR), maximum plasma concentration (C_{max}), time for reaching maximum plasma concentration (t_{max}), mean residence time (MRT), quantifiable and total area under the concentration time curve (AUC), apparent clearance (CL), apparent distribution volume (Vd). In addition, for descriptive purposes, the time courses of FVIII:C and OCTA12 may be analyzed compartmentally assuming a linear, open, one- or two-compartment model. Exposure levels will be reported untransformed and standardised for dose and body weight.
- In addition, for patients from Cohorts 1 to 3 and Cohort 6: FVIII:C trough and peak levels during, and after for Cohorts 1 and 2, the 3-month daily dosing will be graphically displayed and listed by patient.

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- In addition, for patients from Cohort 3: Estimation of relative bioavailability of FVIII:C by the ratios of AUC after sc administration over AUC after iv administration.
- Data from Cohort 5 covering the pharmacokinetics after single sc doses of 20, 40 and 60 IU/kg OCTA101 will be used to derive estimates of the dose-proportionality of the pharmacokinetics of FVIII:C and OCTA12.
- Quantifiable and λ_z-extrapolated time courses of the concentrations after single doses (all cohorts) will be used to simulate the time courses when defined doses would be administered repeatedly at specified interval.

The total annualized bleeding rate, the spontaneous annualized bleeding rate, the traumatic annualized bleeding rate, the total annualized treated bleeding rate, the spontaneous annualized treated bleeding rate, and the annualized joint bleeding rate during the daily sc treatment with OCTA101 will be presented for patients in the FAS and PP set in Cohort 6, grouped by dose level of daily OCTA101 dosing. These bleeding rates will be compared descriptively to those derived from the bleeding frequencies in the previous 6 months prior to the study. For the daily dosing period of Cohorts 1 to 3, no bleeding rates were calculated, because none occurred during daily prophylaxis with OCTA101. The observation period was considerably shorter than planned due to the study stop.

FLOW CHART OF ASSESSMENTS

Flow Chart 1: Screening Visit Assessments – all patients

Informed consent	X
Eligibility criteria	X
Demographics	X
AB0 blood type	X
CD4$^+$ count	X
Medical history	x
Details on medications taken within one month before screening, including FVIII dosing in the previous 6 months, and any concomitant medications.	x
Body weight	x
Height	x
Physical examination	x
Hemophilia Joint Health Score (HJHS)	x
Target joints	x
Vital signs	x
Routine safety laboratory	x
FVIII inhibitor*	x
AEs	x
Cohort 6: LumiTope assay*	x

* needs to be negative

Flow Chart 2: Cohort 1: Single PK, OCTA101 50 IU/kg sc

	Prior to injection	0.5 h	2 h	4 h	8 h	24 h	48 h	72 h
Body weight	x							
FVIII:C	x	x	x	x	x	x	x	x
OCTA12	x	x	x	x	x	x	x	x
FVIII inhibitor	x							
Anti-OCTA12	x							
Routine lab	x	x			x	x	x	x
Vital signs	x	x			x	x	x	x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection						
AEs and concomitant medication	x	x	x	x	x	x	x	x

Flow Chart 3: Cohort 2: Single PK, OCTA101 100 IU/kg sc

	Prior to injection	0.5 h	2 h	4 h	8 h	24 h	48 h	72 h	96 h
Body weight	x								
FVIII:C	x	x	x	x	x	x	x	x	x
OCTA12	x	x	x	x	x	x	x	x	x
FVIII inhibitor	x								
Anti-OCTA12	x								
Routine lab	x	x			x	x	x	x	x
Vital signs	x	x			x	x	x	x	x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection							
AEs and concomitant medication	x	x	x	x	x	x	x	x	x

Flow Chart 4a: Cohort 3: Single PK, Nuwiq 50 IU/kg iv

	Prior to injection of Nuwiq	0.5 h	2 h	4 h	8 h	24 h	48 h	72 h
Body weight	x							
FVIII:C	x	x	x	x	x	x	x	x
FVIII inhibitor	x							
Routine lab	x	x			x	x	x	x
Vital signs	x	x			x	x	x	x
AEs and concomitant medication	x	x	x	x	x	x	x	x

Flow Chart 4b: Cohort 3: Single PK, OCTA101 50 IU/kg sc into the abdomen

	Prior to injection of OCTA101		2 h	4 h	8 h	12 h	24 h	48 h	72 h
Body weight	x								
FVIII:C	x		x	x	x	x	x	x	x
OCTA12	x		x	x	x	x	x	x	x
Anti-OCTA12	x								
Routine lab	x				x	x	x	x	x
Vital signs	x				x	x	x	x	x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection							
AEs and concomitant medication	x		x	x	x	x	x	x	x

Flow Chart 5 Cohort 4: Single PK, OCTA101 50 IU/kg sc into the thigh

Cancelled

Flow Chart 6a: Cohort 5: Single PK, OCTA101 20 IU/kg sc

	Prior to injection		2 h	4 h	8 h	12 h	24 h	48 h	72 h
Body weight	x								
FVIII:C	x		x	x	x	x	x	x	x
OCTA12	x		x	x	x	x	x	x	x
FVIII inhibitor	x								
Anti-OCTA12	x								
Routine lab	x				x	x	x	x	x
Vital signs	x				x	x	x	x	x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection							
AEs and concomitant medication	x		x	x	x	x	x	x	x

Flow Chart 6b: Cohort 5: Single PK, OCTA101 40 IU/kg sc

	Prior to injection		2 h	4 h	8 h	12 h	24 h	48 h	72 h
Body weight	x								
FVIII:C	x		x	x	x	x	x	x	x
OCTA12	x		x	x	x	x	x	x	x
FVIII inhibitor									
Anti-OCTA12									
Routine lab	x				x	x	x	x	x
Vital signs	x				x	x	x	x	x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection							
AEs and concomitant medication	x		x	x	x	x	x	x	x

Flow Chart 6c: Cohort 5: Single PK, OCTA101 60 IU/kg sc

	Prior to injection		2 h	4 h	8 h	12 h	24 h	48 h	72 h	4 weeks
Body weight	x									
FVIII:C	x		x	x	x	x	x	x	x	
OCTA12	x		x	x	x	x	x	x	x	
FVIII inhibitor										x
Anti-OCTA12										x
Routine lab	x				x	x	x	x	x	
Vital signs	x				x	x	x	x	x	
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection								
AEs and concomitant medication	x		x	x	x	x	x	x	x	

Flow Chart 7: Cohorts 1, 2 and 3, daily injections of OCTA101 approximately 40-60 IU/kg sc for 3 months

	Start of daily treatment with OCTA101	Month 0.5	Month 1	Month 2	Month 3
Body weight	x[1]				
Vital signs	x[1,2]	x[1,2]	x[1,2]	x[1,2]	x[1,2]
Routine safety laboratory	x[1,2]	x[1,2]	x[1,2]	x[1,2]	x[1,2]
FVIII inhibitor	x[1]	x[1]	x[1]	x[1]	x[1]
Anti-OCTA12	x[1]	x[1]	x[1]	x[1]	x[1]
FVIII:C	x[1,2]	x[1,2]	x[1,2]	x[1,2]	x[1,2]
OCTA12	x[1,2]	x[1,2]	x[1,2]	x[1,2]	x[1,2]
Physical examination (Cohort 3 only)					x[3]
Assessment of local injection site reactions	Directly after injection and 15 ± 5 min post-injection, for each injection				
Adverse events	x	x	x	x	x
Concomitant medication	x	x	x	x	x

[1], before injection

[2], 3 h and 6 h after injection

[3], 6 h after injection

Flow Chart 8: Cohorts 1 and 2, PK assessment following 3-month daily administration

	Prior to injection		2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	120 h	7 days	14 days	21 days
Body weight	x													
FVIII:C	x		x	x	x	x	x	x	x	x	x			
OCTA12	x		x	x	x	x	x	x	x	x	x	x	x	x
FVIII inhibitor	x													x
Anti-OCTA12	x													x
Physical examination														x
Assessment of local injection site reactions		Directly after injection and 15 ± 5 min post-injection												
AEs and concomitant medication	x		x	x	x	x	x	x	x	x	x	x	x	x

Flow Chart 9: Cohort 6: 6-7 months daily prophylactic treatment with 12.5 IU/kg OCTA101 sc, then 6-7 months 25 IU/kg OCTA101 sc, probably followed by 40 IU/kg OCTA101 – depending on the results of earlier dosing phases

				For each 6-7 months daily prophylactic treatment period with OCTA101							
	Screening	Nuwiq iv Prophylaxis (4 to 6 weeks)	Start of daily treatment with OCTA101	Month 0.5	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Final Visit
Informed consent	x										
Eligibility criteria	x										
Demographics (age, ethnic origin)	x										
Blood type (AB0)	x										
$CD4^+$ count	x										
Medical history	x										
Previous concomitant medication, incl. FVIII during last 6 months	x										
Body weight	x		x	x	x	x	x	X	x	x	
Vital signs	x		$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	
Routine safety laboratory	x		$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	x
FVIII inhibitor	x		x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x
Anti-OCTA12	x		x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x
FVIII:C level			$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	$x^{1,2}$	
OCTA12	x		x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x
Physical examination, incl. HJHS and target joint assessment	x									x	x
LumiTope assay	x^{1}		x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x^{1}	x
Assessment of local injection site reactions			Directly after injection and 15 ± 5 min post-injection, for each injection								
Bleeding episodes, including respective Nuwiq treatment, if any		x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x

[1], before injection; [2], 8 h after injection

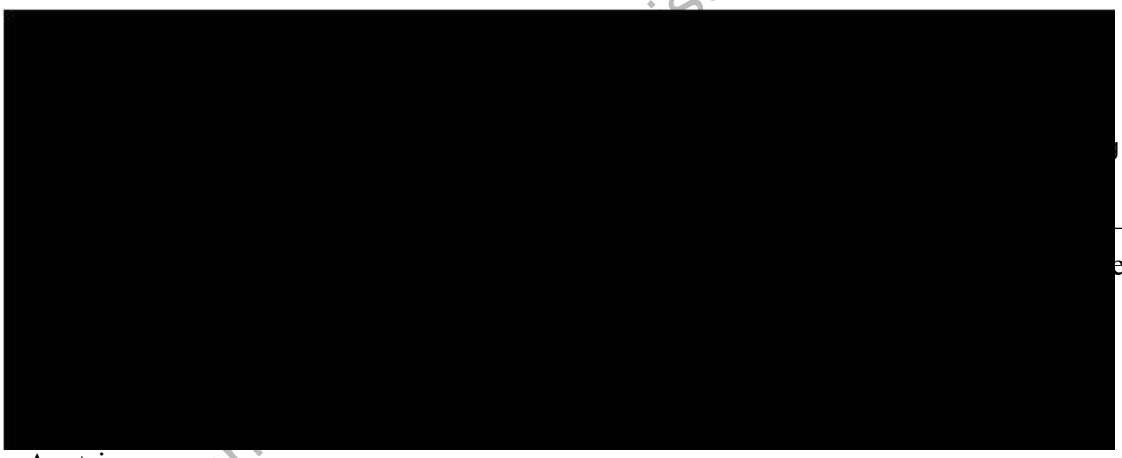
PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

Signature of the Author of the Protocol/Clinical Project Manager

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.



2021 | 15:14:01 CE

Austria

Signature of the Biostatistician

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

2021 | 09:07:02 C

Germany

Signature of the Coordinating Investigator

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

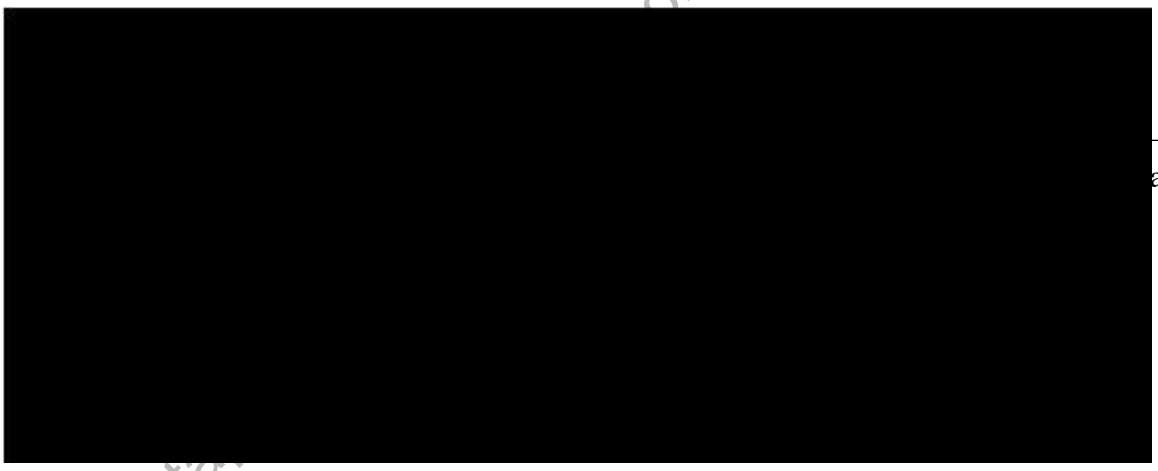


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TABLE OF CONTENTS

STUDY OUTLINE **2**
FLOW CHART OF ASSESSMENTS **21**
PROTOCOL SIGNATURES **27**
TABLE OF CONTENTS **31**
LIST OF ABBREVIATIONS **34**
1 INTRODUCTION **36**
1.1 BACKGROUND 36
1.2 INVESTIGATIONAL MEDICINAL PRODUCT – OCTA101 37
1.3 RATIONALE FOR CONDUCTING THE STUDY 37
1.4 DOSE RATIONALE 37
1.5 BENEFIT-RISK STATEMENT 38
2 STUDY OBJECTIVES **41**
2.1 PRIMARY OBJECTIVE 41
2.2 SECONDARY OBJECTIVES 41
3 INVESTIGATIONAL PLAN **41**
3.1 PRIMARY AND SECONDARY ENDPOINTS 41
3.1.1 Primary Endpoints *41*
3.1.2 Secondary Endpoints *41*
3.2 OVERALL STUDY DESIGN AND PLAN 42
3.3 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUP(S) 46
3.3.1 Study Design *46*
3.3.2 Control Group *47*
3.3.3 Study Parameters *47*
4 STUDY POPULATION **47**
4.1 POPULATION BASE 47
4.1.1 Inclusion Criteria *47*
4.1.2 Exclusion Criteria *48*
4.2 PRIOR AND CONCOMITANT THERAPY 48
4.2.1 Permitted Concomitant Therapy *48*
4.2.2 Forbidden Concomitant Therapy *48*
4.3 WITHDRAWAL AND REPLACEMENT OF PATIENTS 49
4.3.1 Patient Withdrawal *49*
4.3.2 Patient Replacement Policy *49*
4.4 ASSIGNMENT OF PATIENTS TO TREATMENT GROUPS 49
4.5 RELEVANT PROTOCOL DEVIATIONS 49
4.6 SUBSEQUENT THERAPY 50
5 INVESTIGATIONAL MEDICINAL PRODUCTS **50**
5.1 CHARACTERIZATION OF INVESTIGATIONAL PRODUCTS 50
5.1.1 OCTA101 ..... *50*
5.1.2 Nuwiq *50*
5.2 PACKAGING AND LABELLING 50

5.3 CONDITIONS FOR STORAGE AND USE 50
5.4 DOSE AND DOSING SCHEDULE 50
5.5 PREPARATION AND METHOD OF ADMINISTRATION 52
5.6 BLINDING, EMERGENCY ENVELOPES, AND BREAKING THE STUDY BLIND 52
5.7 TREATMENT COMPLIANCE 52
5.7.1 Drug Dispensing and Accountability 52
5.7.2 Assessment of Treatment Compliance 53
6 STUDY CONDUCT 53
6.1 OBSERVATIONS BY VISIT 53
6.1.1 Screening Visit – All Patients 53
6.1.2 Cohort 1 patients – single dose PK, OCTA101 50 IU/kg sc 54
6.1.3 Cohort 2 patients – single dose PK, OCTA101 100 IU/kg sc 55
6.1.4 Cohort 3 patients – single dose PK, PK Nuwiq 50 IU/kg iv, followed by OCTA101 50 IU/kg sc into the abdomen 55
6.1.5 Cohort 4 patients – single dose PK, OCTA101 50 IU/kg sc into the thigh 56
6.1.6 Cohort 5 patients – single dose PK of OCTA101 20 IU/kg sc, followed by single dose PK of OCTA101 40 IU/kg sc, followed by single dose PK of OCTA101 60 IU/kg sc 56
6.1.7 Cohort 1, 2 and 3 patients – daily injections for 3 months, OCTA101 40 - 60 IU/kg sc 57
6.1.8 Cohort 1 and 2 patients – PK assessment following 3-month daily prophylaxis 57
6.1.9 Cohort 6: Following a 4-6 week prophylactic treatment phase with ~30 IU/kg Nuwiq iv 3 x weekly, patients start 6-7 months daily treatment with 12.5 IU/kg OCTA101 sc, then 6-7 months daily 25 IU/kg OCTA101 sc (and probably 40 IU/kg OCTA101 sc, depending on the results of earlier treatment phases) 58
6.1.10 Unscheduled visits 59
6.1.11 Final visits 59
6.1.12 Time Windows Used in this Study, including Tolerances 59
6.2 DURATION OF STUDY 60
6.2.1 Planned Duration for an Individual Patient 60
6.2.2 Planned Duration for the Study as a Whole 60
6.2.3 Premature Termination of the Study 60
7 ASSESSMENTS AND METHODS 61
7.1 DEMOGRAPHIC AND BASELINE INFORMATION 61
7.1.1 Demographic and baseline characteristics 61
7.1.2 Medical history and prior/concomitant medications 62
7.2 EFFICACY ASSESSMENTS 62
7.2.1 Assessments for Secondary Efficacy Endpoints 62
7.3 SAFETY ASSESSMENTS 64
7.3.1 Assessments for Safety Endpoints 64
7.3.2 Adverse Events (AEs) 64
7.3.3 Serious Adverse Events (SAEs) 66
7.3.4 SAE Reporting Timelines 67
7.3.5 Laboratory Tests 68
7.3.6 Vital Signs and Physical Examination 69
7.3.7 Other Relevant Safety Information 70
7.4 OTHER ASSESSMENTS 70

7.4.1 Local injection site reactions *70*
7.5 APPROPRIATENESS OF MEASUREMENTS 71
8 DATA HANDLING AND RECORD KEEPING 71
8.1 DOCUMENTATION OF DATA 71
8.1.1 Source Data and Records *71*
8.1.2 Case Report Forms *72*
8.1.3 Changes to Case Report Form (eCRF) Data *72*
8.2 INFORMATION TO INVESTIGATORS 72
8.3 RESPONSIBILITIES 73
8.4 INVESTIGATOR'S SITE FILE 73
8.5 PROVISION OF ADDITIONAL INFORMATION 74
8.6 INDEPENDENT DATA MONITORING COMMITTEE 74
9 STATISTICAL METHODS AND SAMPLE SIZE 74
9.1 DETERMINATION OF SAMPLE SIZE 74
9.2 STATISTICAL ANALYSIS 74
9.2.1 Populations for Analysis *75*
9.2.2 Efficacy Analysis Plan *75*
9.2.3 Safety Analysis Plan *77*
9.2.4 Handling of Missing Data *78*
9.3 RANDOMIZATION, STRATIFICATION, AND CODE RELEASE 78
9.4 INTERIM ANALYSIS 78
10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS 78
10.1 ETHICAL/REGULATORY FRAMEWORK 78
10.2 APPROVAL OF STUDY DOCUMENTS 79
10.3 PATIENT INFORMATION AND INFORMED CONSENT 79
10.4 PROTOCOL AMENDMENTS 79
10.5 CONFIDENTIALITY OF PATIENT DATA 79
11 QUALITY CONTROL AND QUALITY ASSURANCE 80
11.1 PERIODIC MONITORING 80
11.2 AUDIT AND INSPECTION 80
12 REPORTING AND PUBLICATION 80
12.1 CLINICAL STUDY REPORT 80
12.2 PUBLICATION POLICY 80
13 LIABILITIES AND INSURANCE 81
14 REFERENCES 81
15 APPENDICES 82
A. APPENDIX 1: DIAGRAM OF SUBCUTANEOUS INJECTION SITES 82

LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse drug reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area Under the Concentration-Time Curve
BE	Bleeding episode
BMI	Body mass index
BU	Bethesda unit
CHMP	Committee for Medicinal Products for Human Use
CL	Apparent clearance
C_{max}	Maximum Plasma Concentration
CRO	Contract Research Organisation
CV	Coefficient of variation
CVAD	Central venous access device
DLT	Dose-limiting toxicities
DMC	Independent Data Monitoring Committee
eCRF	Electronic Case Report Form
ED	Exposure day
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FVIII	Coagulation factor VIII
FVIII:C	Factor VIII coagulation activity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Human-cl rhFVIII	Human-derived recombinant FVIII protein product
IB	Investigator Brochure
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITI	Immune tolerance induction
ITT	Intention-To-Treat
IU	International Unit
iv	Intravenous
IVR	In vivo recovery
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

MRT	Mean residence time
NCA	Non-compartmental individual PK analyses
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
PTP	Previously-treated patient
PUP	Previously-untreated patient
r(h)FVIII	Recombinant (human) FVIII
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SDV	Source data verification
SOC	System organ class
t_{max}	time for reaching maximum plasma concentration
Vd	Apparent distribution volume
VWF	Von Willebrand Factor

1 INTRODUCTION

1.1 Background

Hemophilia A is a serious coagulation disorder caused by a deficiency in FVIII that predisposes sufferers to recurrent bleeding, particularly in the joints. Hemophilia A is associated with significant morbidity and, if left untreated, can be life-threatening, particularly in patients who develop neutralizing FVIII inhibitors to FVIII replacement therapy. Hemophilia A is currently treated with replacement FVIII therapy with plasma-derived products or rFVIII products, such as simoctocog alfa, either prophylactically or on-demand. Prophylaxis is the gold-standard treatment for patients with severe hemophilia, and should be implemented as early as possible. Prophylaxis has been shown to significantly reduce bleeding rates, preserve joint health, and reduce the risk of intracranial hemorrhages (the most serious bleeding event for babies) and inhibitors, compared with on-demand treatment. Adherence to a prophylactic regimen is essential to ensure that the prevention of bleeding is realized.

All currently available FVIII replacement products are administered via intravenous (iv) infusion, which usually involves infusion three times per week or every other day. The frequency/complexity of administration is one of many factors that influences adherence to hemophilia treatment. The iv route of administration is unpleasant for patients, often requires trained medical assistance, and is potentially damaging to the structure of the vein in the long term. In small babies, venous access is often particularly challenging, hindering the use of prophylaxis in children at a very young age despite the benefit for bleed protection. These drawbacks can result in reduced compliance by patients and are not very conducive to the development of regular, prophylactic care regimes, leaving patients open to the danger of bleeds and the resulting detrimental health consequences. In many patients, particularly children, a central venous access device (CVAD) is implanted, which is however associated with a risk of thrombosis, infection, and mechanical failure.

Subcutaneous (sc) administration of rFVIII opens new perspectives for the treatment of hemophilia with the potential to change current care paradigms. sc delivery provides a more convenient, low-volume and less intensive mode of delivery for patients, and avoids CVAD-related complications. This will most likely improve compliance with treatment and the care of patients with hemophilia A. In addition, early prophylaxis in very young children will become feasible and patients on episodic treatment may be encouraged to switch to a prophylaxis regimen that will improve joint outcomes and quality of life. To be clinically viable, sc delivery for FVIII therapy in hemophilia A must overcome the limitation of poor FVIII bioavailability and ensure that the desired plasma level of FVIII is achieved. Von Willebrand factor (VWF), which naturally protects FVIII from proteolytic degradation, represents a promising candidate to increase the sc bioavailability of rFVIII. FVIII is naturally associated with VWF in the circulation and this increases the half-life of FVIII from 2-3 hours to 12-14 hours. When administered alone sc, the recovery of FVIII that reaches circulation is too low for an economic and effective treatment. One major cause for low recovery is the binding of FVIII to phospholipids that are present on cell surfaces at the site of injection.

The concept for development of OCTA101 is to combine recombinant FVIII with a fragment of recombinant VWF that includes the FVIII-binding domains and thereby shields the FVIII phospholipid-binding domain. By building on more than 50 years of experience using iv FVIII to correct the FVIII deficiency in patients with hemophilia A, OCTA101 has the potential to

provide the first and only self-administered, sc "true FVIII" therapy for hemophilia based on a human cell-line derived rFVIII for direct replacement.

1.2 Investigational Medicinal Product – OCTA101

OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer) is composed of OCTA8 (Human-cl rhFVIII – Nuwiq Intermediate 2 Q-Eluate) and OCTA12 (recombinant human VWF fragment dimer), mixed in a defined molar ratio of approximately 1:3 (1:6 with regards to FVIII binding sites in OCTA12, as one OCTA12 dimer contains two FVIII binding sites).

The rFVIII in OCTA101, OCTA8, is derived from the commercial Nuwiq (simoctocog alfa) manufacturing process. Nuwiq is manufactured in a human cell line and was approved by EMA in 2014 and by the FDA in 2015 for the treatment of hemophilia A based on data in previously treated patients (PTPs). Interim data for 66 previously untreated patients (PUPs) treated for ≥20 exposure days in the meanwhile completed NuProtect study have subsequently been published (Liesner et al. 2018). The cumulative inhibitor rate with Nuwiq was 20.8% (12.8% high titer), which compares with 44.5% (28.4% high titer) for rFVIII products produced in hamster cell lines reported in the recently published SIPPET study (Cannavò et al. 2017).

Studies in minipigs indicate a sc bioavailability of 46% and an apparent terminal half-life of 25.3 hours, approximately 3.6-fold longer than after iv administration. In a hemophilia A dog model, similar results were obtained (bioavailability: 30.3%; 3.3-fold half-life prolongation). In both animal models, peak levels of FVIII:C were observed after approximately 6 hours. Clinically relevant in-vivo hemostatic function of OCTA101 was demonstrated in an animal model. For a summary of non-clinical results, please refer to the Investigator Brochure (IB).

1.3 Rationale for Conducting the Study

To initiate clinical development of OCTA101, this study will be a dose escalation study in adults with the main purpose to assess the safety of OCTA101, but also to gain knowledge about its PK characteristics, the dose proportionality, and the sc bioavailability compared with iv administration of Nuwiq, in order to define the prophylactic treatment (dose per injection and injection interval) that would result in protective trough levels of FVIII:C for future Phase 3 studies in adolescents/adults and children.

This Phase 1/2 study will provide data regarding safety, the time course of FVIII:C plasma and OCTA12 concentration after repeated daily sc injections of a fixed dose for 6-7 months (at 2, probably 3, different dose levels in Cohort 6), and whether these FVIII:C levels protect against bleeding episodes. The experience gained in this study may lead to an adaption of the PK-based dose calculations for the pivotal Phase 3 studies.

This study will be conducted according to ICH-GCP.

1.4 Dose Rationale

One part of the study was to be a single ascending dose study in 4 cohorts:

- Cohort 1: 50 IU/kg
- Cohort 2: 100 IU/kg
- Cohort 3: 200 IU/kg

- Cohort 4: 400 IU/kg

Based on the results of the animal studies, the proposed doses (50, 100, 200, and 400 IU/kg) were expected to result in measurable FVIII:C plasma levels up to approximately 2 to 4 days after injection. The highest dose planned to be tested (400 IU/kg) would certainly be significantly higher than the highest prophylactic dose earlier assumed to be tested in the pivotal Phase 3 studies (based on simulations derived from animal data an initial dose of approximately 114 IU/kg followed by daily doses of approximately 60 IU/kg would be needed to maintain a trough level of at least 10%) and would provide a safety margin in case of inadvertent administration of higher prophylactic doses in the later stages of clinical development. In addition, based on the available animal data, a conservative IVR of around 0.17 [IU/dL]/[IU/kg] was expected. Thus, with a dose of 400 IU/kg, FVIII plasma level of around 70% was expected. These levels would not pose a risk to patients. On the contrary, depending on t_{max} or time to 80% t_{max}, also break-through bleeds during prophylaxis might possibly be treated with OCTA101 with no further need of iv FVIII infusions for the patient.

Dose proportionality of OCTA101 was evaluated after single sc administration of three different doses (50 IU/kg, 100 IU/kg and 200 IU/kg) in 4 additional patients (Cohort 5).

The DMC assessed the data after each cohort and recommend continuation, modification or stopping of the study. Based on the results from Cohorts 1 and 2, the sponsor and DMC decided that escalation to higher doses should not take place and that further characterization of 50 IU/kg and lower doses was warranted. Therefore, Cohort 3 received 50 IU/kg administered into the abdomen, Cohort 4 was cancelled, and Cohort 5 investigated dose linearity at a lower dose range than initially planned (20, 40 and 60 IU/kg instead of 50, 100 and 200 IU/kg). Patients in Cohort 3 also received a single iv dose of 50 IU/kg Nuwiq in order to compare the bioavailability of sc OCTA101 with those of Nuwiq injected iv. In Cohort 5, four patients each were consistently injected with OCTA101 either in the abdomen or in the thigh at all three dose levels.

In order to evaluate the safety, efficacy, and PK of OCTA101 after repeated doses, with the revised study design, patients from Cohort 1, 2, and 3 received daily dosing (approximately 40-60 IU/kg, with the dose chosen to allow administration by a single injection; it was permitted to daily alternate the vial size, e.g. 3000 IU on one day 1, 5000 IU on day 2, 3000 IU on day 3, 5000 IU on day 4 etc.) of OCTA101 for 3 months. A new cohort will also investigate 12.5 IU/kg OCTA101 sc daily for 6-7 months and with DMC agreement at each stage, the patients will then proceed to 25 IU/kg (and probably 40 IU/kg) OCTA101 sc daily for a further 6-7 months. Throughout the prophylaxis parts of the study, FVIII inhibitors (including LumiTope assay), plasma concentrations of FVIII:C, and OCTA12 will be measured repeatedly. Bleeding episodes should be treated with Nuwiq.

As discussed in the Benefit-Risk Statement below, based on the accumulated data from the study, an additional cohort, Cohort 6, will investigate lower doses of 12.5 and 25 IU/kg (and probably 40 IU/kg) OCTA101 sc daily for 6-7 months each, based on DMC recommendations.

1.5 Benefit-Risk Statement

The nonclinical program has shown that rFVIII combined with OCTA12 effectively enters the circulation, that it has a prolonged half-life and a clinically relevant in-vivo hemostatic function. No overt toxicity or adverse effects were observed, with a safety margin of at least 10 times the clinical dose. See the IB for details.

Patients would benefit if the clinical development of OCTA101 was to prove successful as sc delivery of FVIII provides a more convenient and less intrusive mode of administration for patients, and may improve treatment compliance.

As OCTA101 consists of Nuwiq-process-derived rhFVIII (Q-eluate, the penultimate step of the Nuwiq drug substance manufacturing process) and the recombinant VWF fragment dimer, OCTA12, the risks that can be expected in patients consist of those known for Nuwiq, with further possible risks those associated with OCTA12 and with sc administration.

The risks for Nuwiq have been well established and are outlined in the Nuwiq Investigator Brochure. The most frequently occurring adverse reactions (>0.5%) in clinical trials were paresthesia, headache, injection site inflammation, injection site pain, non-neutralizing anti-factor VIII, inhibitor formation (only in PUPs), back pain, vertigo, dry mouth, hemorrhagic anemia, dizziness, malaise, and dyspnea. Hypersensitivity reactions, including anaphylaxis, are possible.

There are no known risks associated with OCTA12. OCTA12 per se has no hemostatic function except that it binds to FVIII with a Kd comparable to endogenous VWF. There was no evidence of adverse effects attributable to OCTA12 in Cynomolgus monkeys after repeated sc injections of OCTA101.

Subcutaneous administration has generally proven to have fewer risks as compared to iv administration. The most common adverse reactions related to sc administration consist of local injection site reactions, with pain, bruising, bleeding, itching, redness, or swelling at the injection site. Repeated injections at the same spot can cause scarring and hardening of fatty tissue that may interfere with uptake of sc-administered medication. Nevertheless, no relevant local intolerance reactions were observed in a repeated dose toxicity study in Cynomolgus monkeys.

To minimize risk in this first-in-human study, one part of the study planned to include a single ascending dose portion in 4 cohorts. This part of the study was to identify a safe and effective dose for testing in further clinical trials. The results from Cohort 1 showed that a dose of 50 IU/kg OCTA101 was effective in raising FVIII:C plasma levels while no safety issues were observed. In Cohort 2 (100 IU/kg), FVIII inhibitor formation was observed in 2 patients, one after 1 month and one after 2 months of daily treatment with OCTA101, without the occurrence of bleeding episodes, resulting in the study being placed on study hold. Immune tolerance induction (ITI) treatment was initiated with Nuwiq and the patients were followed-up. One patient died in summer 2020, after a fatal adverse event, the second patient is still undergoing ITI treatment.

One patient from Cohort 3 also developed low titer transient FVIII inhibitors after 3 months of prophylaxis with OCTA101 (first month) and Nuwiq (second and third month). This FVIII inhibitor was transient. The patient returned to his previous FVIII concentrate and wasn't tested being inhibitor positive, again. Based on the results from Cohorts 1, 2, and 3, the sponsor and DMC decided that escalation to higher doses should not take place and that further characterization of the 50 IU/kg dose and lower doses for daily prophylaxis was instead warranted. The stopping rules for the study were amended to add detailed instructions on how inhibitor formation should be monitored and how any further inhibitor formation will impact study conduct. The study design was amended accordingly with protocol Amendments 2 and 3. Data will be continuously monitored, and the DMC consulted, where required throughout the remainder of the study.

It was noted that a major difference between treatment of Cohort 1 and Cohort 2 patients was the iv treatment with Nuwiq of all patients of Cohort 1 during the period between the first PK with sc OCTA101 and the start of daily prophylactic sc administration of OCTA101 at a dose of 50 IU/kg. In contrast, all patients of Cohort 2 underwent sc treatment with OCTA101 directly after the first PK assessment, without any interim Nuwiq dosing. It was also noted that patients from both cohorts were treated mainly on-demand with a plasma-derived product before entering the study.

Immune response upon sc application of FVIII with or without iv pre-treatment with FVIII as applied for Cohorts 1, 2, and 3 respectively, has been evaluated in a humanized hemophilic mouse model described by Reedtz-Runge et al. (2018). The applied humanized hemophilic E17 HLA-DRB1*1501 mice model carries a knockout of the entire murine MHC class II complex. It expresses a chimeric murine-human MHC class II complex, which contains the sequences of the human HLA-DRA*0101 and HLADRB1*1501 proteins responsible for peptide binding, and the murine binding sides for the murine CD4 protein (T-cell surface glycoprotein, coreceptor for MHC class II molecule:peptide complex). This humanized hemophilic mice was characterized by Steinitz et al. (2012) and appeared to be very sensitive against sc treatment using a full-length recombinant FVIII: all mice treated sc with FVIII developed anti-FVIII antibodies. Upon iv administration of FVIII, only a fraction of mice developed anti-FVIII antibodies (between 30%-80%).

Reedtz-Runge et al. (2018) used this mice model to evaluate the hypothesis, if iv administration of recombinant FVIII (Advate) generates immune tolerance to sc administered glycopegylated FVIII (N8GP). The humanized hemophilic mice were treated sc with N8GP with or without iv pre-treatment with Advate. They administered iv Advate to 10 mice at a dose of 500 IU/kg once weekly over an 8-week period. After this they started an 8-week challenge period with sc N8GP, also 500 IU/kg (but only in mice who did not develop antibodies to iv FVIII; n=5). Mice that did not develop antibodies to iv FVIII therapy, did not develop any antibodies to N8GP upon sc-treatment.

These data from a humanized hemophilic mouse model suggest that iv pre-treatment of patients with Nuwiq may have induced tolerance for subsequent sc treatment with OCTA101. Therefore, for the newly added Cohort 6, all patients will receive a 4 to 6-week run-in period with 3 x weekly ~30 IU/kg Nuwiq iv prophylaxis. Patients will also have to have a negative LumiTope test result at screening. This will exclude patients who have non-inhibitory antibodies, which can play a role in subsequent development of inhibitory antibodies.

Patients with FVIII inhibitors had received OCTA101 doses of 100 IU/kg sc for PK determination followed by 50 IU/kg daily dosing. With 50 IU/kg OCTA101, a mean trough FVIII plasma level of more than 10% was achieved and protected patients from breakthrough bleeds. PK modelling based on the PK data obtained from Cohorts 1 and 3, indicate that doses lower than 50 IU/kg should provide sufficient bleeding control. With 12.5 IU/kg, FVIII trough plasma levels of more than 1% are expected based on modelling, which should protect the patients from breakthrough bleeds. Therefore, following the Nuwiq iv prophylaxis run-in, Cohort 6 will investigate daily prophylaxis with 12.5 IU/kg for 6-7 months, followed by 25 IU/kg (and probably 40 IU/kg) for 6-7 months, based on DMC recommendations.

By introducing a run-in with Nuwiq iv prophylaxis and testing lower doses of OCTA101 sequentially in ≥16 patients in total, the risk of inhibitor formation should be substantially reduced. However, inhibitor formation will be monitored carefully in Cohort 6, and the study

will be terminated if one more patient develops a confirmed FVIII inhibitor (≥0.6 BU) as determined by the central lab.

In conclusion, the existing nonclinical data and the clinical data from Cohorts 1,2, 3 and 5, together with the risk minimization steps implemented in this protocol, indicate that participating in this study should not represent any additional risk to the included patients beyond the possibility of inhibitor formation, for which risk mitigation steps have been taken.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the safety of various doses of OCTA101 after sc injection.

2.2 Secondary Objectives

The secondary objectives of this study are to assess

- the pharmacokinetics of FVIII:C after single sc injection of OCTA101
- the dose proportionality of FVIII:C after sc injections of different doses of OCTA101
- the bioavailability of sc OCTA101 compared to iv injection of Nuwiq
- the pharmacokinetics of OCTA12 (recombinant human von Willebrand Factor fragment dimer) after single injection of OCTA101
- plasma trough and peak levels of FVIII:C after daily injections of OCTA101
- plasma trough and peak levels of OCTA12 after daily injections of OCTA101
- the efficacy of sc injections of OCTA101 in preventing bleeding episodes.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoints

The following safety endpoints are the primary endpoints in this study:

- Adverse events
- DLTs
- Thromboembolic events
- Local injection site reactions
- Inhibitor formation to FVIII

3.1.2 Secondary Endpoints

Efficacy:

- PK parameters of FVIII:C (AUC, C_{max}, T_{max}, IVR, $t_{1/2}$, MRT, CL [iv dosing only], Vd [iv dosing only])

- PK parameters of OCTA12 (same parameters as for FVIII:C above)
- Total annualized bleeding rate during daily sc treatment with OCTA101
- Spontaneous annualized bleeding rate during daily sc treatment with OCTA101
- Total annualized treated bleeding rate during daily sc treatment with OCTA101
- Spontaneous annualized treated bleeding rate during of daily sc treatment with OCTA101
- Traumatic annualized bleeding rate during of daily sc treatment with OCTA101
- Annualized joint bleeding rate during daily sc treatment with OCTA101
- FVIII:C trough and peak plasma levels during daily dosing
- Score (4-point rating scale) to assess efficacy of treatment of bleeding episodes with Nuwiq

Safety:

- Antibody formation to OCTA12
- LumiTope assay results
- OCTA12 plasma levels during daily dosing
- Routine lab tests compared to baseline
- Vital signs compared to baseline
- Physical examination results compared to baseline

3.2 Overall Study Design and Plan

SubQ8-01 is a first-in-human, prospective, open-label Phase 1/2 study of OCTA101, which consists of an eluate of an already authorized human recombinant coagulation factor FVIII product (Nuwiq®) along with OCTA12 (at a molar ratio of 1:6, with regards to FVIII binding sites in OCTA12), a recombinant human VWF fragment dimer, which is expected to increase the bioavailability of FVIII on sc dosing. The trial will be carried in adult patients with severe hemophilia A according to a staged integrated design with five planned consecutive cohorts. No patient can receive treatment in more than 1 cohort.

One part of the study was to be a single ascending dose study in 4 cohorts (50, 100, 200 and 400 IU/kg). The decision of going to the next higher dose was to be taken after each cohort by an external independent DMC after review of safety and tolerability data, FVIII:C plasma levels, and PK characteristics of FVIII:C and OCTA12. Any safety-relevant signals were also forwarded to the DMC for their review as they occurred. The reason(s) for not progressing to a higher dose level, e.g. dose-limiting toxicities (DLTs), were to be documented if such a decision was reached.

Pre-defined DLTs for this study are:

1. Severe allergic reactions at least possibly related to study drug.
2. Severe vital organ toxicity at least possibly related to study drug that does not resolve to at least mild severity within 48 to 72 hours.
3. Any treatment-emergent severe toxicity at least possibly related to study drug other than the toxicities referenced in 2) that does not decrease to mild or resolve within 7 days

Definitions for mild, moderate and severe toxicity:

Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Based on the results from Cohorts 1 and 2, the sponsor and DMC decided that escalation to higher doses should not take place and that further characterization of 50 IU/kg and lower doses was warranted. Therefore, Cohort 3 received 50 IU/kg administered into the abdomen, Cohort 4 was to receive 50 IU/kg administered into the thigh (this was not proceeded with, as described below), and Cohort 5 investigated dose linearity at a lower dose range than initially planned (20, 40 and 60 IU/kg instead of 50, 100 and 200 IU/kg).

Patients in Cohort 3 also received a single iv dose of 50 IU/kg Nuwiq in order to compare the bioavailability of sc OCTA101 with those of Nuwiq (the FVIII part of OCTA101) injected iv. The treatment sequence was Nuwiq followed by OCTA101.

Dose proportionality of OCTA101 was evaluated after single sc administration of three different doses (20 IU/kg, 40 IU/kg and 60 IU/kg) in 4 additional patients (Cohort 5).

Following completion of the PK assessments in Cohort 3 and 1-month into OCTA101 daily prophylaxis in this cohort, the study was put on hold due to inhibitor development in a second patient (in Cohort 2).

Due to the study hold, patients in Cohort 3 were switched to prophylaxis with Nuwiq after having received 1-month of OCTA101 daily prophylaxis. Patients in Cohort 3, completed the study when their overall time on daily prophylaxis (OCTA101 + Nuwiq) reached 3 months. By the time of preparation of protocol version 8.0, Cohorts 1, 2 (with the exception of 1 patient with FVIII inhibitors who entered ITI treatment with Nuwiq), 3, and 5 were completed (in Cohort 5 only 4 of the planned 8 patients were treated). During study hold, at the recommendation of the DMC, detailed immunogenicity analyses were carried out, including the LumiTope assay, and all available data were presented to the DMC.

With the agreement of the DMC, it was decided to proceed with the study introducing the following changes to the study design. Cohort 4 was cancelled and Cohort 5 was cut from 8 patients to 4.

A new cohort (Cohort 6) was planned with 16 evaluable patients. In this cohort, around 18-20 patients (to compensate for possible early drop-outs) were planned to start with an initial 4 to 6-week run-in treatment period with Nuwiq iv prophylaxis followed by 12.5 IU/kg OCTA101 sc daily prophylaxis for >3 up to 6-7 months. With DMC agreement, the patients were planned to proceed to 25 IU/kg OCTA101 sc daily prophylaxis for 6-7 months. Based on the results of both dosing phases, a 40 IU/kg OCTA101 were planned to be considered.

Cohort 6 was planned to proceed as follows:

- Following completion of the run-in period with Nuwiq iv prophylaxis, 3 patients (one screened patient withdrew consent after Nuwiq run-in phase) started daily dosing with 12.5 IU/kg OCTA101 sc.

- After 3 months of treatment with OCTA101, the patients will have their 3-month follow-up visit. During the 2 to 3 weeks waiting for all relevant results, especially FVIII inhibitor testing results, these patients will continue on daily dosing with 12.5 IU/kg OCTA101 sc.
- If the DMC determines that further patients can start their daily prophylaxis with OCTA101, at least 16 patients will proceed with 12.5 IU/kg OCTA101. After a further 3 months, following DMC data review, the first 3 patients of this cohort will start on daily dosing with 25 IU/kg OCTA101 sc for 6-7 months. The remaining patients will follow after a further 3 months, after DMC data review.
- Patients reporting two spontaneous bleeding episodes will be switched to the next higher dose level after having completed at least 3 months with 12.5 IU/kg OCTA101 daily treatment: they will start daily dosing with 25 IU/kg OCTA101 sc.
- Depending on the results of the 12.5 IU/kg and 25 IU/kg OCTA101 treatment phases, the initiation of a 40 IU/kg OCTA101 phase will be considered together with the DMC.
- Bleeding episodes will be controlled with the use of Nuwiq during the entire duration of treatment in Cohort 6.

The cohorts are summarized as follows:

- Cohort 1: 50 IU/kg (n=4): single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing.
- Cohort 2: 100 IU/kg (n=4): single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing.
- Cohort 1 and 2 (n=8): single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 120 hours after dosing for FVIII and up to 21 days for OCTA12.
- Cohort 3: 50 IU/kg (n=8): two-period investigation of a single iv dose of 50 IU/kg Nuwiq profiled for up to 72 hours after dosing followed by sc dose of 50 IU/kg OCTA101 administered into the abdomen profiled up to 72 hours. Treatments were to be administered in fixed sequence, with Nuwiq first.
- Cohort 4: 50 IU/kg (n=4): Cancelled.
- Cohort 5 (n=4): three-period investigation of single sc doses of 20, 40, and 60 IU/kg OCTA101 profiled up to 72 hours after dosing, respectively. Treatments were to be administered in fixed dose-ascending sequence.
- Cohort 6 (n ≥16): Following an initial 4 to 6-week run-in period with Nuwiq iv prophylaxis, >3-6 months daily prophylactic treatment with 12.5 IU/kg OCTA101 sc, then 25 IU/kg OCTA101 sc for a further 6-7 months (exact dosing depends on available vial sizes). In case of two spontaneous bleeding episodes, after having completed at least 3 months with 12.5 IU/kg OCTA101 daily treatment the individual treatment dose was planned to be increased from 12.5 to 25 IU/kg. Site of administration (abdomen or thigh) to be chosen by the patient. A further treatment phase with 40 IU/kg OCTA101 was planned to be discussed with the DMC, once results of earlier dosing phases are available.
  The DMC will review and assess the available results approximately every 3 months.

By DMC-recommendation, patients enrolled in Cohorts 1, and 2 proceeded to the 3-month prophylactic treatment part of the study and received daily dosing (approximately 40-60 IU/kg;

dose chosen to allow administration by single injection; it was permitted to daily alternate the vial, e.g. 3000 IU on one day 1, 5000 IU on day 2, 3000 IU on day 3, 5000 IU on day 4 etc.) of OCTA101 for 3 months (home treatment). Patients from Cohort 1 received prophylactic Nuwiq (home treatment) until the DMC had confirmed that OCTA101 could be used as daily prophylaxis. Bleeding events during the study were treated with Nuwiq. Throughout this part of the study, FVIII inhibitors, plasma concentrations of FVIII:C, and OCTA12 were measured repeatedly.

A PK assessment was to be performed in all patients from Cohorts 1 and 2 who completed their 3-month daily injection period; it was actually performed in all patients of Cohort 1 and in one patient of Cohort 2 (the two inhibitor patients as well as a patient whose FVIII levels were very low did not do the repeat PK assessment).

Independent expert evaluation by the DMC has steered study progress for the stepwise dosage increments by cohort and the progression of patients from the first three cohorts to 3-month daily dosing. In addition, the DMC has advised on changes of the proposed dosage for the assessment of bioavailability (Cohort 3) and dose-proportionality (Cohort 5) and changes in the schedule of PK blood sampling and/or the duration of profiling. These changes have been implemented with Amendment 2 of the protocol. Based on the observation of a second patient with inhibitors in Cohort 2, the DMC recommended placing the study on hold. The DMC recommended restarting the study with the implementation of Amendment 3, which cancelled Cohort 4, cut Cohort 5 to 4 patients instead of the planned 8, and introduced Cohort 6 investigating lower doses of OCTA101 sc daily prophylaxis per dose level following a run-in period with Nuwiq iv prophylaxis. The DMC will continue to be involved in the further conduct of the study.

This study started in Q2 2019 and is planned to be completed by Q3 2022.

Summary of status at the time of finalizing the amended study protocol version 9.0:

At the time of finalizing the amended study protocol version 9.0, the following had been completed:

- Cohort 1: 50 IU/kg: single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing – completed as planned in 4 patients. 3-month OCTA101 daily dosing – completed as planned in 4 patients. PK assessment after 3-month daily dosing – completed as planned in 4 patients.
- Cohort 2: 100 IU/kg: single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing – completed as planned in 4 patients. 3-month OCTA101 daily dosing – completed as planned in 2 patients; 2 patients with inhibitors in Cohort 2 discontinued daily OCTA101 prophylaxis and started ITI treatment with Nuwiq. PK assessment after 3-month daily dosing – completed as planned in 1 patient; not performed in the 2 inhibitor patients switched to ITI treatment and a patient with low levels of FVIII. One patient who developed FVIII inhibitors and started ITI died after a fatal serious adverse event (retroperitoneal hematoma). The second patient undergoing ITI after FVIII inhibitor development is continuing treatment with Nuwiq.
- Cohort 3: 50 IU/kg (n=8): two-period investigation of a single iv dose of 50 IU/kg Nuwiq profiled for up to 72 hours after dosing followed by sc dose of 50 IU/kg OCTA101 administered into the abdomen profiled up to 72 hours – completed as

planned in 8 patients. 3-month OCTA101 daily dosing – due to the study hold, patients in Cohort 3 were switched to prophylaxis with Nuwiq after having received about 1-month of OCTA101 daily prophylaxis; the 8 patients in Cohort 3 completed the study when their overall time on daily prophylaxis (OCTA101 + Nuwiq) reached 3 months.

- Cohort 4: 50 IU/kg (n=4): cancelled.
- Cohort 5 (n=4): three-period investigation of single sc doses of 20, 40, and 60 IU/kg OCTA101 profiled up to 72 hours after dosing with 4-week follow-up visit – completed in 4 patients instead of the originally planned 8 patients.
- Cohort 6 (n≥16): Nineteen patients were screened for Cohort 6 since autumn 2020, of whom two failed inclusion-/exclusion criteria, and two withdrew consent. Ten patients started daily treatment with 12.5 IU/kg OCTA101 after a 4-6 weeks prophylactic treatment run-in phase with Nuwiq, 3 times weekly. Further five patients started the 4-6 weeks run-in phase, but they have not yet started treatment with OCTA101.

  After six month daily treatment with OCTA101 a positive FVIII inhibitor result (0.8°BU/mL) was reported for patient C6-Q1-01-02 on 14-Jul-2021. After consultation and in agreement with the DMC the sponsor decided to put the study on-hold with immediate effect: all patients with OCTA101 treatment were switched back to prophylactic treatment with Nuwiq, 3 times weekly. On 27-Jul-2021 a further low-titer FVIII inhibitor was reported for patient C6-Q1-01-10 (1.6 BU/mL).

  It was decided to stop all further treatment with OCTA101, but to offer all enrolled patients access to Nuwiq prophylactic treatment until they are integrated into the National Health Insurance program for haemophilia A patients, again, but no longer than until the end of September 2021 + 2 weeks time window.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

The study evaluates i) the safety, tolerability and pharmacokinetics of single sc doses of OCTA101; ii) the absolute bioavailability of FVIII following sc dosing of OCTA101; iii) the dose relationship of the FVIII-exposure levels (20-60 IU/kg OCTA101); and iv) the safety, efficacy, tolerability and trough PK levels of a prophylactic 3-month treatment with once daily sc dosing of approximately 40-60 IU/kg OCTA101 (based on DMC recommendations).

As discussed in Section 1.5 and implemented by Amendment 3 to this protocol, the study design has been adapted based on the observation of inhibitor formation in Cohort 2. In Cohort 6, 12.5 IU/kg OCTA101, followed by 25 IU/kg (and probably 40 IU/kg) OCTA101 daily prophylaxis will be investigated in a cohort of ≥16 patients following a run-in period with Nuwiq iv prophylaxis.

The bioavailability and dose proportionality comparisons, together with the PK data from the single ascending dose cohorts, will determine the prophylactic treatment (dose per injection and injection interval) that would result in protective trough levels of FVIII:C for Phase 3 studies in adolescents/adults and children.

By DMC-recommendation, patients from Cohorts 1, 2 and 3 received daily dosing (home treatment) with approximately 40-60 IU/kg of OCTA101 for 3 months. Throughout this part of the study, FVIII inhibitors, plasma concentrations of FVIII:C, and OCTA12 will be measured

repeatedly. This part of the study will provide safety data for multiple doses and the time course of FVIII:C and OCTA12 plasma concentrations after repeated daily injections. These data will allow determination of whether these FVIII levels protect against bleeding episodes and of the dynamics of OCTA12.

A PK assessment was performed in patients from Cohorts 1 and 2 who completed their 3-month daily injection period further characterizing the PK of FVIII:C and OCTA12. Blood samples will be collected up to 21 days in order to see a decline in OCTA12 plasma concentrations (and allow determination of half-life) as the initial PK period is not long enough to see a decline of OCTA12. Concomitant measurement of FVIII:C up to 120 h will allow evaluation of any interaction between OCTA12 plasma concentration and FVIII:C. The experience gained in this part of the study may lead to an adaption of the PK-based dose calculations for the Phase 3 studies.

3.3.2 Control Group

Patients in Cohort 3 will also receive a single iv dose of 50±5 IU/kg Nuwiq in order to compare the bioavailability of sc OCTA101 with those of Nuwiq injected iv. To be clinically viable, sc delivery of FVIII therapy in hemophilia A must overcome the limitation of poor FVIII bioavailability and ensure that the desired plasma level of FVIII is achieved. As Nuwiq is the rFVIII component of OCTA101, it is the appropriate control for bioavailability of OCTA101.

3.3.3 Study Parameters

The safety and efficacy parameters selected for assessment in this study are well-established parameters that have been used in the Nuwiq clinical studies that led to marketing authorization of that product, and they will establish the safety and pharmacokinetics of sc administered OCTA101.

Based on the observation of inhibitor formation during the study, further analysis of antibody formation using the LumiTope assay was introduced by Amendment 3.

4 STUDY POPULATION

4.1 Population Base

The study will include adult male patients with severe hemophilia A who have been previously treated with FVIII.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Severe hemophilia A (<1% FVIII:C) as documented in medical records
2. Males ≥18 years of age
3. Subjects who have had ≥150 exposure days (EDs) with a FVIII product
4. Written informed consent for study participation obtained before undergoing any study specific procedures

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

1. Previous participation in this trial
2. Use of an Investigational Medicinal Product within 30 days prior to the first OCTA101 injection
3. History of FVIII inhibitors titer ≥0.6 BU/mL defined by medical records
4. Inhibitors to FVIII (≥0.6 BU/mL) at screening measured by Nijmegen modified Bethesda method at central laboratory
5. Human immunodeficiency virus (HIV) positive subjects with a $CD4^+$ count <200/mL
6. Clinically significant anemia at screening (hemoglobin <8 g/dL)
7. Presence of any significant comorbidity (at the discretion of the investigator) that might confound the interpretation of the study data and/or that might put the patient at undue risk by participating in the trial
8. Any coagulation disorder other than hemophilia A
9. AST or ALT levels >3 times the upper limit of normal
10. Creatinine >120 µmol/L
11. Platelet count <100,000 µL
12. BMI ≥30 kg/m²
13. For Cohort 6, patients with a positive LumiTope test at screening will be excluded.

4.2 Prior and Concomitant Therapy

Details on medications taken within one month before screening, including FVIII dosing in the previous 6 months, and any concomitant medications taken during the study must be recorded in the eCRF.

4.2.1 Permitted Concomitant Therapy

Concomitant therapies not interfering with the objectives of the study are permitted.

Details of any concomitant medication must be recorded in the electronic Case Report Form (eCRF).

Any bleeding episodes occurring between the Screening Visit and the first exposure with OCTA101 (or Nuwiq in Cohort 6 patients) should be treated with the patient's previously used FVIII concentrate.

Similarly, prophylactic treatment between the Screening Visit and the first exposure with OCTA101 (or Nuwiq in Cohort 6 patients) should be treated with the patient's previously used FVIII concentrate.

4.2.2 Forbidden Concomitant Therapy

With the exception of the Nuwiq run-in in Cohort 6, no FVIII concentrate other than OCTA101 should be given for prophylaxis and no FVIII concentrate other than Nuwiq should be given for treatment of bleeding episodes (except for emergency situations).

Patients who switch to another FVIII product during their study participation will not be considered treatment failures in the efficacy analyses if:

- the use of another FVIII concentrate was due to an emergency (example: accident requiring treatment with FVIII without the patient [or intensive care unit personnel] having access to the IMP)
- the IMP was not available to the patient in time (example: patient experiences severe bleed but has not enough product available at home)

4.3 Withdrawal and Replacement of Patients

4.3.1 Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation (Termination Visit). If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients who are to undergo more than 1 PK assessment but drop out before the entire PK assessment is completed (i.e. Cohorts 3 and 5) will be replaced. If data indicate that IMP was inadvertently administered iv instead of sc for the PK assessment, the patient will be replaced. Any replacement patient will be assigned to the same treatment sequence as the withdrawn patient.

Patients withdrawn from the study for safety reasons will not be replaced.

Patients who were screened but did not proceed to OCTA101 treatment can be included after re-screening.

4.4 Assignment of Patients to Treatment Groups

The Investigator will enter a unique identifier of each patient in both the eCRF and the confidential patient identification list. The numbers will be allocated sequentially in the order in which the patients are enrolled. Patients will be assigned to the next available treatment cohort in a sequential manner. The Investigator will inform the sponsor representative of new patients enrolled using a subject enrolment form and faxing or e-mailing it to the Clinical Study Monitor or to the Clinical Project Manager immediately.

Under no circumstances are patients who enroll in the study permitted to re-enroll.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

4.6 Subsequent Therapy

Any patient who discontinues from the study or completes study treatment as planned should continue medical treatment according to local standards.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Characterization of Investigational Products

5.1.1 OCTA101

OCTA101 (Human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer) is composed of rFVIII (derived from commercial Nuwiq) and the recombinant VWF fragment dimer OCTA12, at a molar ratio of 1:6 (with regards to FVIII binding sites in OCTA12).

OCTA101 will be provided as lyophilized powder in vials containing 500 IU, 750 IU, 1000 IU and 2000 IU (additional 3000 IU and 5000 IU vials were provided for the completed cohorts 1°-°5) human recombinant coagulation factor FVIII. Each vial needs to be reconstituted with 1.0 mL of Water for Injection, which will be provided in a pre-filled glass syringe. The batch number(s) used will be recorded. The final product will be released by the responsible Octapharma Quality Control Department, in accordance with a defined final product specification.

5.1.2 Nuwiq

Nuwiq will be used in this study and will be provided by Octapharma. Nuwiq will be provided as lyophilized powder in vials containing either 500, 1000, 2000, or 3000 IU. Each vial needs to be reconstituted with 2.5 mL of Water for Injection. Nuwiq should be injected iv by bolus injection at a maximum rate of 4 mL/min. The batch number(s) used will be recorded.

5.2 Packaging and Labelling

This open-label study design does not necessitate the blinding of study participants or study site personnel with respect to treatment information.

OCTA101 and Nuwiq will be packed and labelled according to local regulations, ensuring that the final labelling will comply with the national requirements of each country where the study is conducted.

5.3 Conditions for Storage and Use

OCTA101 and Nuwiq have to be stored at 2-8°C protected from light. They must not be frozen.

The Investigator/authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

The following will be administered at the study site by trained personnel:

- Cohort 1: Single injection of OCTA101 50 IU/kg sc with 72 hours of observation.

- Cohort 2: Single injection of OCTA101 100 IU/kg sc with 96 hours of observation.
- Cohort 1 and 2: PK assessment after 3-month daily dosing: Single injection of OCTA101 50 IU/kg sc with 120 hours of observation for FVIII and 21 days of observation for OCTA12.
- Cohort 3: Single injection of Nuwiq 50 IU/kg iv with 72 hours of observation, followed by single injection of OCTA101 50 IU/kg sc administered into the abdomen with 72 hours of observation.
- Cohort 4: (Cancelled) Single injection of OCTA101 50 IU/kg sc administered into the thigh with 72 hours of observation.
- Cohort 5: Single injection of OCTA101 20 IU/kg sc with 72 hours of observation, followed by single dose of OCTA101 40 IU/kg sc with 72 hours of observation, followed by single dose of OCTA101 60 IU/kg sc with 72 hours of observation.
- Cohort 6: 4-6 weeks prophylactic run-in treatment phase with ~30 IU/kg Nuwiq iv, given 3 x weekly, followed by 2 (probably 3) phases of 6-7 months daily injection with OCTA101, first 12.5 IU/kg, followed by 25 IU/kg daily (and probably 40 IU/kg). No wash-out periods are required between the treatment phases. Patients reporting two spontaneous bleeding episodes during the 12.5 IU/kg treatment phase may immediately switch to the 25 IU/kg daily, if they have completed at least 3 months with 12.5 IU/kg. Nuwiq (according to SmPC) is used to control bleeding episodes, if any.

In all cases, the minimum number of injections required to provide the required dose must be administered. If multiple injections are needed, then they should not be administered at the same spot. The PK doses were to be achieved as accurately as possible with the available vial strengths as a single injection; it was permitted to daily alternate the vial size, (e.g. 3000 IU on one day 1, 5000 IU on day 2, 3000 IU on day 3, 5000 IU on day 4 etc.).

OCTA101 will be administered by sc injection into the abdomen or thigh (see Appendix 1 in Section 13.a), whereby for Cohorts 1 and 2 the choice is up to the investigator and patient, in Cohort 3 all administrations of OCTA101 will be into the abdomen, in Cohort 5, four patients each will consistently be injected with OCTA101 either in the abdomen or in the thigh at all three dose levels.

In Cohort 6, the choice is up to the patient. It is recommended to alternate injection sites.

Patients will be trained on the correct method for sc administration. In Cohort 1, 2 and 3, daily injections of OCTA101, approximately 40-60 IU/kg sc, were planned to be administered by the patient for 3 months.

Cohort 6 will investigate 6-7 months daily prophylactic treatment with 12.5 IU/kg OCTA101 sc, then 25 IU/kg OCTA101 sc for a further 6-7 months (and probably 40 IU/kg OCTA101), administered by the patients, unless the patient is attending a visit at the study site.

At the end of the daily injection period in Cohorts 1 and 2, and after a wash-out of at least 72 hours after the last OCTA101 injection, or any other FVIII injection, the PK of FVIII:C and OCTA12 was to be assessed with an OCTA101 dose of 50 IU/kg. FVIII:C and OCTA12 levels were to be measured up to 120 hours; thereafter, additional samples will be taken to measure OCTA12 at the following time points: 7, 14 and 21 days. After the 120 hour time point patients could use Nuwiq for prophylaxis or treatment of bleeding episodes until the last sampling time point.

Nuwiq was to be injected iv once for PK evaluation at a dose of 50 IU/kg in patients of Cohort 3.

Patients in Cohort 1 who had completed their respective PK assessment used Nuwiq (iv) at the discretion of the investigator for prophylaxis until the DMC had adjudicated 50 IU/kg as safe, had advised to continue with Cohort 2, and had advised that Cohort 1 patients can start daily dosing with OCTA101.

During study hold, the patients in Cohort 3 stopped OCTA101 daily prophylaxis after about 1 month and were switched to Nuwiq prophylaxis during the study hold period. Patients in Cohort 3 completed the study when they had completed 3 months of daily prophylaxis in total (OCTA101 + Nuwiq). Two patients with inhibitors entered ITI treatment with Nuwiq and did not receive the planned treatment for Cohort 2.

Bleeding events during the study will be treated with Nuwiq in accordance with the recommended doses given in the SmPC.

5.5 Preparation and Method of Administration

OCTA101 and Nuwiq will be provided in single-use vials to be reconstituted in Water for Injection.

Prior to injection, the solution must have reached room temperature, without taking any specific warming-up measures. The preparation should be used immediately after reconstitution. The solution is a clear or slightly opalescent colorless solution. Solutions that are cloudy or have deposits must not be used.

OCTA101 must be injected sc into the abdomen or thigh (see Appendix 1 in Section 13.a). The site of sc administration must be documented. The investigator and the patients will receive detailed Handling Instructions on how and where to perform the sc injections.

Nuwiq must be injected iv by bolus injection (maximally 4 mL/minute) by using aseptic technique.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable in this open-label study.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP dispensed to patients. A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of IMP received and dispensed to each patient and the remaining quantity.

For their home treatment, a sufficient amount of OCTA101 and of Nuwiq will be handed out to the patients. The Investigator or his/her designee has to document the date, quantities and batch (lot) number(s) of IMP handed out including the corresponding patient number. The patients will be advised to return used or expired vials to the study site at their on-site visits, and to return used and unused vials at the (early) Termination Visit.

Patient returned IMP (used or unused) must not be used anymore and must be destroyed after completion of drug accountability.

The inventory and dispensing log will be available to the monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

5.7.2 Assessment of Treatment Compliance

Administration of IMP at the study site will be performed by trained personnel, who will document details of administration in the eCRF.

At the first visit, the Investigator will provide eligible patients with a sufficient amount of trial medication (in cooling boxes, if appropriate).

Eligible patients will receive a patient diary after the first injection of OCTA101 (after the first injection of Nuwiq for the run-in in Cohort 6). The investigator will explain to the patient how to fill in the diary and will emphasize the importance of carefully documenting all treatment details, adverse events, and concomitant medications. Furthermore, the efficacy rating criteria for treating a bleeding episode (Section 7.2.1.1) and the criteria for assessing the severity of a bleed will be explained. The Investigator will emphasize the necessity of careful documentation of all treatment details. The recording of at-home injections will include the date and time, dose, and batch number. IMP is provided with tear-off labels that must be placed in the diary.

In case of treatment of BEs, the patients will document the site and severity of the bleed, the start and end dates and time, and carry out an efficacy assessment according to the explanation provided in the diary. The patients will be trained on how to administer Nuwiq to control bleeding, if required.

Study product administrations that are overseen by the Investigator (e.g. treatment in case of severe BEs treated at the study site), are to be documented in the patient's journal (by the Investigator), as well as in the patient's diary (by the patient).

In addition, the patient will record any concomitant medications taken during the study period in their diaries.

For each follow-up visit at the study site, the patients must bring all diaries to be reviewed and validated by site personnel.

6 STUDY CONDUCT

The flow charts of assessments by study visit are given, starting on page 21. The flow chart of the recently ongoing Cohort 6 can be found on page 26.

6.1 Observations by Visit

6.1.1 Screening Visit – All Patients

The following assessments will be performed during the Screening Visit, which should take place within 30 days before the first administration of IMP:

- Obtaining voluntarily given, written (signed and dated) informed consent
- Check of inclusion and exclusion criteria
- Demographics: age, ethnic origin
- Blood type (ABO)
- $CD4^+$ count
- Medical history
- Details on medications taken within one month before screening, including FVIII dosing in the previous 6 months, and any concomitant medications.
- Body weight
- Height
- Physical examination
- Hemophilia Joint Health Score (HJHS)
- Target joint(s) (defined as three or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding screening visit)
- Vital signs: systolic and diastolic blood pressure, body temperature, pulse (before blood sample collection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay)
- Routine safety lab: Hematology: red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count; Clinical chemistry: total bilirubin, ALT, AST, urea, serum creatinine, lactate dehydrogenase
- Start of monitoring of adverse events (AEs)
- Cohort 6: LumiTope assay (negative test result required)

Any bleeding episodes occurring between the Screening Visit and the first exposure to OCTA101 or Nuwiq should be treated with the patient's previously used FVIII concentrate.

Following screening, eligible patients will receive a patient diary after the first injection of OCTA101 or Nuwiq. The investigator will explain to the patient how to fill in the diary and will emphasize the importance of carefully documenting all treatment details, adverse events, and concomitant medications.

PK assessments are to be performed after a washout period of at least 72 h, if possible, from the last FVIII injection. Patients must not be experiencing any bleeding.

6.1.2 Cohort 1 patients – single dose PK, OCTA101 50 IU/kg sc

The following assessments will be performed:

- Body weight (before injection)
- Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h and 72 h after injection)
- Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h and 72 h after injection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
- Blood sample for anti-OCTA12 measurement (before injection)

- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after injection).
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.3 Cohort 2 patients – single dose PK, OCTA101 100 IU/kg sc

The following assessments will be performed:

- Body weight (before injection)
- Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection)
- Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
- Blood sample for anti-OCTA12 measurement (before injection)
- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection).
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.4 Cohort 3 patients – single dose PK, PK Nuwiq 50 IU/kg iv, followed by OCTA101 50 IU/kg sc into the abdomen

NUWIQ injection (iv): the following assessments will be performed:

- Body weight (before injection)
- Vital signs (before injection, 0.5 h, 8 h, 24 h, 48 h, and 72 h after injection)
- Routine safety lab (before injection, 0.5 h, 8 h, 24 h, 48 h, and 72 h after injection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before injection)
- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, and 72 h after injection.
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

OCTA101 injection (sc into the abdomen): the following assessments will be performed:

- Blood sample for anti-OCTA12 measurement (before injection)
- Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after injection)
- Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after injection)

- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection).
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.5 Cohort 4 patients – single dose PK, OCTA101 50 IU/kg sc into the thigh

Cancelled.

6.1.6 Cohort 5 patients – single dose PK of OCTA101 20 IU/kg sc, followed by single dose PK of OCTA101 40 IU/kg sc, followed by single dose PK of OCTA101 60 IU/kg sc

OCTA101 injection 20 IU/kg into the abdomen (4 patients): the following assessments will be performed:

- Body weight (before injection)
- Vital signs (before injection, 8 h, 12 h, 24 h, 48 h and 72 h after the injection)
- Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h and 72 h after the injection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection)
- Blood sample for anti-OCTA12 measurement (before the injection)
- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

OCTA101 injection 40 IU/kg into the abdomen (4 patients): the following assessments will be performed:

- Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

OCTA101 injection 60 IU/kg into the abdomen (4 patients): the following assessments will be performed:

- Vital signs (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Routine safety lab (before injection, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay) 4 weeks after injection
- Blood sample for anti-OCTA12 measurement 4 weeks after injection
- Blood samples for measurement of FVIII:C (one-stage and chromogenic assay) (before the injection and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after the injection)
- Blood samples for measurement of OCTA12, as above for FVIII:C
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.7 Cohort 1, 2 and 3 patients – daily injections for 3 months, OCTA101 40 - 60 IU/kg sc

Patients entering the 3-month daily prophylactic part will be trained in sc self-administration of study medication. Patients in Cohort 1 will be required to return to the study site for their first daily dose; patients in Cohorts 2 and 3 will still be present at the study site at the time of their first daily dose. The following assessments will be performed:

- Vital signs (before and 3 h and 6 h after the injection at the beginning of the 3-month daily dosing and 0.5, 1, 2, and 3 months thereafter)
- Routine safety lab (before and 3 h and 6 h after the injection at the beginning and 2, 4, 8 and 12 weeks thereafter)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection and 0.5, 1, 2 and 3 months thereafter)
- Blood sample for anti-OCTA12 measurement, (before the first injection and 0.5, 1, 2 and 3 months thereafter)
- Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 3 h and 6 h after the injection at the beginning and 0.5, 1, 2, and 3 months thereafter)
- Blood sample for OCTA12 measurement, (before and 3 h and 6 h after injection at the beginning and 0.5, 1, 2, and 3 months thereafter)
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection, for each injection)
- Physical examination (at End of Study) (Cohort 3 only)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.8 Cohort 1 and 2 patients – PK assessment following 3-month daily prophylaxis

Patients from Cohorts 1 and 2 completing the 3-month daily prophylactic part will attend the study site. The following assessments will be performed:

- After a wash-out of at least 72 hours after the last OCTA101 injection, or any other FVIII injection, a dose of 50 IU/kg OCTA101 sc will be administered
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before and at 21 days after the injection)
- Blood sample for anti-OCTA12 measurement, (before and at 21 days after the injection)
- Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, 72 h, 96 h, and 120 h after the injection)
- Blood sample for OCTA12 measurement, (before and 2 h, 4 h, 8 h, 24 h, 48 h, 72 h, 96 h, 120 h, 7 days, 14 days, and 21 days after the injection)
- Physical examination (at End of Study)
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection)
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.9 Cohort 6: Following a 4-6 week prophylactic treatment phase with ~30 IU/kg Nuwiq iv 3 x weekly, patients start 6-7 months daily treatment with 12.5 IU/kg OCTA101 sc, then 6-7 months daily 25 IU/kg OCTA101 sc (and probably 40 IU/kg OCTA101 sc, depending on the results of earlier treatment phases)

Patients in Cohort 6 will have their first Nuwiq administered at the study site. After the run-in period, patients will be trained in sc OCTA101 self-administration for subsequent home treatment.

The following assessments will be performed:

Start of 4 to 6 week Nuwiq run-in:

- Documentation of bleeding episodes and their treatment throughout the run-in period
- Adverse event monitoring throughout the run-in period
- Documentation of concomitant medication throughout the run-in period

Daily OCTA101 treatment periods:

- Vital signs (before and 8 h after the injection OCTA101 at the beginning of each dosing period and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)
- Routine safety lab (before and 8 h after the OCTA101 injection at the beginning of each dosing period and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)
- Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay), (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each of the 6-7 month OCTA101 daily prophylaxis treatment periods)
- Blood sample for anti-OCTA12 measurement, (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each of the 6-7 month OCTA101 daily prophylaxis treatment periods)
- Blood sample for FVIII:C measurement (one-stage and chromogenic assay), (before and 8°h after the OCTA101 injection at the beginning of the 6-7 months dosing periods and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter)

- Blood sample for OCTA12 measurement, (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each dosing period)
- Physical examination (at End of Study)
- LumiTope assay (before the first injection of OCTA101 and 0.5, 1, 2, 3, 4, 5 and 6 months thereafter for each dosing period)
- Assessment of local injection site reactions (directly after injection and 15 ± 5 min post-injection, for each injection)
- Documentation of bleeding episodes and their treatment throughout the study period
- Adverse event monitoring throughout the study period
- Documentation of concomitant medication throughout the study period

6.1.10 Unscheduled visits

In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations due to severe bleeding episodes.

6.1.11 Final visits

All patients will immediately stop treatment with OCTA101, if another patient develops a confirmed FVIII inhibitor (≥0.6 BU).

In this case, all FVIII inhibitor negative patients will switch to prophylactic treatment with Nuwiq comparable to the run-in phase, and will come for a final follow-up visit after treatment change. During the final follow-up visit the following should be done:

• Routine safety lab
• Blood sample for FVIII inhibitor measurement (modified Nijmegen Bethesda assay)
• Blood sample for anti-OCTA12 measurement
• Blood sample for OCTA12 measurement
• Physical examination
• LumiTope assay
• Documentation of bleeding episodes and their treatment
• Adverse event monitoring
• Documentation of concomitant medication

6.1.12 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 2: Time Windows Used in this Study

Time point	Time stated	Tolerance
Interval between visits	x-month daily prophylaxis part: at 0.5, 1, 2, 3, 4, 5 and 6 months	± 4 days
Blood sampling	before IMP administration	≤ 30 minutes
	30 minutes after IMP administration	± 10 minutes
	1–6 hours after IMP administration	± 15 minutes
	7–12 hours	± 1 hour
	13–24 hours	± 2 hours
	> 24-120 hours	± 3 hours
	7 days	± 1 day
	14 days	± 2 days
	21 days	± 3 days
Inhibitor testing	4 weeks	± 1 week

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for an individual patient according to protocol will range from 5 days (patients from Cohort 5) until up to approximately 10 months (patients from Cohort 6), not counting the time period between the screening visit and the first administration of IMP, or patients undergoing immune tolerance induction therapy.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the planned observation period.

The start of the study (enrolment of first patient) was Q2 2019, and the estimated end of the study (last visit of last patient) is Q3 2022.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and IECs/IRBs should be informed in accordance with national regulations.

Early termination of the study as a whole or by center may apply for the following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

- A single death event (with the exception of death from underlying disease or any other death clearly unrelated to OCTA101) that occurs within 30 days of administration of study drug.
- If clinical development of OCTA101 is terminated for any reason.

According to the revised stopping rules implemented by Amendment 2, the study was to be put on hold until a further DMC recommendation for further conduct of the study was made, if more than one patient met the following criteria:

- Exhibits a consistently high titer inhibitor (≥5 BU), as determined by central laboratory tests including a retest as detailed in Section 0.

or

- Exhibits a low titer inhibitor (≥0.6 BU and <5 BU), as determined by central laboratory test, including a retest as detailed in Section 0, and a standard recovery test using intravenous factor VIII shows a recovery below 66%. A formal half-life study with determination of the terminal half-life ($t_{½}$) associated with the recovery study is encouraged with the patient in a non-bleeding state and free of any intercurrent illness.

As a further patient with inhibitors in Cohort 2 subsequently met these criteria, the study was put on hold and patients stopped OCTA101 treatment. The ongoing patients in Cohort 3 were switched to Nuwiq prophylaxis for the remainder of the planned 3-month prophylaxis period.

The study will be terminated if another patient develops an inhibitor (≥0.6 BU).

6.2.3.2 Early Termination at an Individual Study Center

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (IMPs, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The following information will be recorded during the Screening Visit:

7.1.1 Demographic and baseline characteristics

The demographic and baseline characteristics are age, ethnic origin, height, weight, and Body Mass Index (BMI).

Blood type (ABO) will be documented. If not available, this will be tested.

$CD4^+$ count will be determined.

The Hemophilia Joint Health Score (HJHS) will be documented.

Target joint(s) will be documented (defined as three or more spontaneous bleeding episodes into a single joint within 6 consecutive months preceding screening visit).

7.1.2 Medical history and prior/concomitant medications

The medical history will be obtained by interviewing the patient. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

Prior and concomitant medications, including FVIII treatment details in previous 6 months and bleeding frequency will be documented.

7.2 Efficacy Assessments

7.2.1 Assessments for Secondary Efficacy Endpoints

7.2.1.1 Bleeding episode (BE) data to be documented

For any BE occurring during the study, the following data will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor, moderate, major, life-threatening)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- Dates and times Nuwiq was injected, if applicable
- Nuwiq dose(s) and batch number(s)
- Assessment of the efficacy of treatment at the end of the BE; see below

All of these parameters will be documented by the patient (together with the investigator in case of on-site treatments) in the patient diary. Patients who experience a major or life-threatening BE should be treated at the study site.

Definition of BE

If the treatment of a BE at one site is interrupted for more than 48 hours, the events are recorded as two separate BEs; if another than the original bleeding site is affected, the events are recorded as separate BEs at any time.

If there are several simultaneous bleeding sites, each bleeding site is recorded as a separate BE.

For certain major bleeding events, e.g., iliopsoas bleeds or bleeding into target joints, it may be necessary to continue treatment beyond the resolution of the acute phase to prevent recurrent hemorrhage. These additional infusions should be recorded in the diary (and eCRF) but will not be evaluated as treatments of the BE.

Assessment of the efficacy of treatment at the end of a BE

At the end of a BE, treatment efficacy will be assessed by the patient (together with the investigator in case of on-site treatment) using the following predefined criteria:

- **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 2 infusions for complete resolution
- **None**: No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution

The proportion of BEs **successfully treated** with Nuwiq will be evaluated for all BEs together and by severity. All efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

7.2.1.2 FVIII:C plasma levels

Blood samples for the assessment of FVIII:C (one-stage and chromogenic assays) plasma levels will be taken at the following timepoints:

- Cohort 1: before injection of OCTA101 50 IU/kg sc, 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, and 72 h after injection.
- Cohort 2: before injection of OCTA101 100 IU/kg sc, 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, 72 h and 96 h after injection.
- Cohort 3: FVIII:C only, before injection of Nuwiq 50 IU/kg iv, 0.5 h, 2 h, 4 h, 8 h, 24 h, 48 h, and 72 h after injection.
- Cohort 3: before injection of OCTA101 50 IU/kg sc, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection.
- Cohort 5: before injection of OCTA101 20 IU/kg sc, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection.
- Cohort 5: before injection of OCTA101 40 IU/kg sc, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection.
- Cohort 5: before injection of OCTA101 60 IU/kg sc, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h after injection.
- Cohort 1, 2, and 3 – daily sc injections for 3 months: before injection of OCTA101 25 IU/kg sc and 3 and 6 h after injection, for the first injection and at 0.5, 1, 2 and 3 months thereafter.
- Cohort 1 and 2 patients – PK assessment following 3-month daily prophylaxis: before injection of OCTA101 50 IU/kg sc, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h 96 h, and 120 h after injection.
- Cohort 6 – daily sc injections for 6-7 months: before injection of OCTA101 12/25 IU/kg sc (and probably 40 IU/kg) and 8 h after injection, for the first injection and at 0.5, 1, 2, 3, 4, 5 and 6 months thereafter in each dosing period. Samples will be shipped to the central laboratory for one-stage and chromogenic assay assessments (see Section 7.3.5).

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) associated with the administration of IMP (for definitions and reporting requirements, see Sections 7.3.2, 7.3.3, and 7.3.4)
- Drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see Section 7.3.7)

7.3.2 Adverse Events (AEs)

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the subject/patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.3, and 7.3.2.4. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed, and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE that is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE that is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

One such 'important medical event' is the development of FVIII inhibitors. Another is the suspected transmission of an infectious agent. These events, therefore, have to be reported as SAEs.

A suspected virus transmission means that virus antigen has been detected in the patient. The passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee:

Martina Jansen
Senior Clinical Project Manager Haematology
Oberlaaerstrasse 235
A – 1100 Vienna
Austria
Phone: +43 1 61032 1208
Mobile: +43 664 80408208
Fax: +43 1 61032 9249
Email: martina.jansen@octapharma.com

The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: +43 1 61032-9949
E-mail: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.5 Laboratory Tests

7.3.5.1 Local Laboratory

The **routine safety laboratory tests** (Hematology: red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, $CD4^+$ count. Clinical chemistry: total bilirubin, ALT, AST, urea, serum creatinine, lactate dehydrogenase) will be done by the local laboratory. The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

7.3.5.2 Central Laboratory

FVIII:C (one-stage and chromogenic assays) and **FVIII inhibitors** will be assessed by the following central laboratory:

Esoterix Inc (Coagulation)
8490 Upland Drive, Suite 100
Englewood, CO 80112, USA

OCTA12 was measured by the following central laboratory (for cohorts 1-5):

SYNLAB Analytics & Services Germany GmbH
Bayerstr. 53
80335 Munich, Germany

Anti-OCTA12 was measured by the following central laboratory (for cohorts 1-5):

SYNLAB Analytics & Services Switzerland AG
Birsfelden, Switzerland

OCTA12 and Anti-OCTA12 is measured by the following central laboratory (for Cohort 6):

Octapharma Pharmazeutika Produktionsges.m.b.H.
Octapharma Clinical Laboratory
Oberlaaer Strasse 235, 1100 Vienna, Austria
Clinical Laboratory: at1kliniklabor@octapharma.com

Inhibitor activity will be determined by the modified Bethesda assay (Nijmegen modification) using plasma-derived FVIII as a test base. Inhibitor tests will be performed at the times specified in Section 6, and whenever inhibitor development is suspected. In case of positive inhibitor results, inhibitor retesting using a second separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result. Patients who develop a non-transient inhibitor and do not agree to start an ITI will be withdrawn from the study. In case of confirmed positive inhibitor, ITI may be initiated with Nuwiq according to the investigator's discretion. Patients developing an inhibitor and starting ITI will be closely monitored, once they have been informed about the ITI treatment details and gave their written consent before ITI

initiation. Depending on the development of the inhibitor, a bi-weekly (later on monthly to 3-monthly) inhibitor titer testing is considered appropriate.

Once the inhibitor is eliminated, a normalized recovery and half-life are expected during the continued ITI. Samples to test the recovery are recommended to be drawn at baseline and 15 minutes post-injection. For the half-life evaluation, the following sampling time points are recommended: baseline, 15 minutes, 3, 6, 9, 12, (24) hours post-injection.

Patients will complete study participation after a complete success of the ITI (inhibitor-free, normalized recovery and half-life), or after a maximum ITI period of 36 months.

In case of development of antibodies to OCTA12, patients will be closely monitored for any clinically relevant signs and symptoms (e.g. lack of efficacy or unusual plasma concentrations of FVIII and/or OCTA12).

The **LumiTope assay** will be performed by the following central laboratory:

University Clinic Bonn
Institute of Experimental Haematology and Transfusion Medicine
Venusberg Campus 1
53127 Bonn, Germany

The LumiTope assay is a sensitive immunoassay based on the Luminex™ system for detection and characterization of anti-FVIII antibodies in patient plasma samples. The Luminex™ technology is a bead-based assay system using superparamagnetic microbeads. Specific proteins (e.g. full-length and BDD FVIII, several single- and multi-domain fragments of the FVIII molecule) are individually coupled to different magnetic bead regions. Each bead contains its own distinct dye ratio which will generate a unique fluorescence pattern to enable individual bead identity. Beads are mixed with the plasma samples and later incubated with a phytoerythrin-conjugated antibody that produces a fluorescence signal proportional to the amount of bound FVIII antibodies. A positive signal in the screening visit sample would exclude a patient from entering the study as the probability of later inhibitor development during OCTA101 treatment may be increased if antibodies are present. The cut-off to differentiate positive and negative LumiTope assay results will be determined according to the publication of Shankar et al (Shankar et al. 2008), which provides recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products.

7.3.6 Vital Signs and Physical Examination

The vital signs obtained at the time points specified in Section 6 are blood pressure, body temperature, pulse rate, and respiratory rate.

Physical examinations will be performed at the visits specified in Section 6. Both height and weight will be measured at baseline. In addition, weight will be measured at all visits prior to dosing.

7.3.7 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the last IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as AE or, if the reaction fulfils one of the criteria for seriousness, as SAE.

b) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

c) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

d) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

e) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of a lack of efficacy may be continued bleeding in a patient with hemophilia following the correct administration of coagulation factors.

7.4 Other Assessments

7.4.1 Local injection site reactions

Patients will evaluate injection site pain using a visual analog scale (VAS) (0 mm/no pain, 100 mm/extreme pain) immediately after injection completion.

Investigator (and patient in case of home treatment) should assess local injection reactivity directly after injection and 15 ± 5 min post-injection as described in ISO10999-10 standard:

- 0=no skin reactivity;
- 1=mild (subject is aware of the signs/symptoms, but finds it easily tolerated)

- 2=moderate (discomfort enough to cause interference with usual activities)
- 3=severe (subject is incapacitated and unable to work or participate in many or all usual activities).

7.5 Appropriateness of Measurements

All measurements used for the assessment of the safety and efficacy of OCTA101 are in compliance with the requirements set up in the CHMP "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009").

All FVIII inhibitor and FVIII plasma level samples obtained in the course of this study will be evaluated by accredited central laboratories using validated methods and assays.

All OCTA12 and anti-OCTA12 antibody samples obtained in the course of this study will be evaluated by a laboratory working according to EMA/INS/GCP/532137/2010, Feb 2012: "Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples", using validated methods.

If clinically indicated, FVIII and inhibitor testing can additionally be performed in the local laboratory. The results obtained locally will be recorded in the eCRFs.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Case Report Form (eCRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. The EDC system will require entering a reason for any change in data unless data is changed immediately after data entry, in which case "Immediate correction" will be written automatically into the audit trail. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing eCRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) is authorized to perform tasks relating to the study.

The central laboratory for all coagulation parameters and inhibitor testing is Esoterix Inc (Coagulation), Englewood, USA.

The central laboratory for measurement of OCTA12 (for cohorts 1-5) was SYNLAB Analytics & Services Germany GmbH, Bayerstr. 53, 80335 Munich, Germany

The central laboratory for measurement of Anti-OCTA12 (for cohorts 1-5) was SYNLAB Analytics & Services Switzerland AG, Birsfelden, Switzerland

The central laboratory for measurement of OCTA12 and anti-OCTA12 in Cohort 6 is Octapharma Clinical Laboratory, Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria

The central lab for LumiTope analysis is University Clinic Bonn, Institute of Experimental Haematology and Transfusion Medicine, Venusberg Campus 1, Bonn, Germany.

Study data management and statistics will be delegated under an agreement of transfer of responsibilities to Metronomia Clinical Research GmbH, Munich, Germany.

All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, using the principles of good clinical practice (GCP) and good laboratory practice (GLP) guidelines, respectively follow the EMA Reflection Paper 2012, SOPs and complying with all other applicable regulations.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established by the Sponsor. The DMC will be composed of recognized experts in the field of hemophilia who are not actively recruiting patients.

The DMC will review relevant data at defined times during the study and will give advice on the continuation, modification, or termination of the study. Any safety-relevant signals will also be forwarded to the DMC for their review as they occur. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the DMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external Contract Research Organization (CRO). All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics. Two separate SAPs will be created: the first one for the final statistical analysis of all available data of enrolled patients in Cohorts 1, 2, 3, and 5 and the second one for the final analysis of the newly defined Cohort 6.

9.1 Determination of Sample Size

The sample size was determined based on pre-clinical findings and clinical reasoning, and was discussed with the FDA. No formal sample size calculation was performed.

9.2 Statistical Analysis

A formal statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

Data collected in this study will be summarized according to their nature as follows:

- Continuous variables: arithmetic mean, standard deviation, minimum and maximum values, median and quartiles depending on the number of observations.
- Categorical variables: absolute and relative frequencies.
- The geometric mean and geometric CV will additionally be included in the descriptive analyses of pharmacokinetic parameters, except for T_{max}.

9.2.1 Populations for Analysis

The **safety analysis set** (SAF) will include all patients who received at least one dose of IMP.

The **full analysis set** (FAS) defined according to the intention-to-treat (ITT) principle will include all patients who received at least one dose of OCTA101 in the context of repeat daily prophylactic dose (approximately 40-60 IU/kg or 12.5/25 IU/kg (and probably 40 IU/kg)).

The **per-protocol (PP) set**, i.e., a subset of the FAS, will exclude patients with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter(s).

- Examples of major and minor protocol deviations will be described in the SAP.
- A final decision about the classification of protocol deviations and their consequences regarding assignment of patients to analysis sets will be made during the data review meeting. Decisions and outcome will be approved by the Sponsor.

Due to the stop of the daily dosing period because of antibody formation, no PP set was defined for the analysis of Cohorts 1 to 3.

The **PK analysis set** will include all patients from the SAF who started the initial PK assessment with OCTA101.

The **PK–PP analysis set** will be a subset of the PK analysis set. It will exclude patients not fully evaluable for PK endpoint. The criteria to exclude any patient from this analysis set will be described in the SAP. A final decision about the inclusion into the PK-PP analysis set will be made during the data review meeting. Decisions and outcome will be approved by the Sponsor.

The analysis of safety will be based on the safety set by cohort.

The analysis of data from the repeat dosing will be based on the FAS as primary analysis and on the PP set as secondary analysis. This analysis will be performed by cohort and overall.

The evaluation of PK data will be based on the PK and on the PK-PP analysis sets.

9.2.2 Efficacy Analysis Plan

Pharmacokinetic data will be analysed separately for each dose cohort.

Blood for the determination of the concentrations of FVIII:C (one-stage and chromo-genic assays) and OCTA12 in plasma will be sampled at scheduled times. The time courses of the plasma concentrations will be analysed non-compartmentally using the following conventions:

- The courses of the concentrations are analysed individually relative to the actual time of sampling (relative to the time of first injection).
- For the analysis, non-quantifiable pre-dose levels will be set equal to zero. In the event of quantifiable levels prior to first dosing, the baseline level will be subtracted from the post-dosing values and the further analysis is focused on the post-dosing changes from baseline.
- Post-dosing values that are either missing or not quantifiable will not be included in the analysis.

- Extrapolations beyond the last quantifiable plasma concentration will only be re-ported if the apparent terminal log-linearity used to this purpose is sufficiently well expressed for at least 3 data points.
- The duration of profiling is adjusted by dose; based on the available experience with rFVIII it may be expected that the quantifiable area under the time course of the concentrations (AUC) is at least 80% of the total i.e. extrapolated AUC.
- The time courses of the plasma concentrations will be summarised descriptively by means of the following non-compartmental metrics:
  - C_{max}: maximum observed concentration
  - T_{max}: time of occurrence of C_{max} after dosing
  - AUC(0-t_z): quantifiable area under the time course of the concentrations de-rived by means of the combined linear/log-linear trapezoidal rule
  - λ_z: apparent terminal log-linear rate constant
  - $t_{½}$: apparent terminal log-linear half-life
  - AUC(t_z-∞): AUC extrapolated beyond the last time point with quantifiable concentrations calculated as $C^*(t_z)/\lambda_z$ in which $C^*(t_z)$ is the concentration at time t_z fitted according to λ_z
  - AUC(0-∞): total AUC = AUC(0-t_z)+ AUC(t_z-∞)
  - $AUC_{extrapolated}$: extent of AUC extrapolation = AUC(t_z-∞)/AUC(0-∞)
  - AUMC(0-t_z) and AUMC(0-∞): quantifiable and total area under the statistical first moment curve
  - MRT: mean residence time = AUMC(0-∞)/AUC(0-∞)
  - IVR: *in vivo* recovery = dose- and body weight-normalised maximum gain in FVIII:C
  - CL: total clearance (iv dosing only) = Dose/AUC(0-∞)
  - Vd: estimated distribution volume (iv dosing only) = CL.MRT
- Exposure levels will be reported untransformed and standardised for dose and body weight.

The same conventions will be used for the plasma concentrations of FVIII:C and OCTA12 sampled after the single dose administration of 50 IU/kg OCTA101 after the completion of the 3 months daily dosing period of Cohort 1 and Cohort 2.

Single-dose data from Cohort 3 comparing the pharmacokinetics after sc and iv dosing (Nuwiq) will be used to derive estimates of the absolute bioavailability after sc dosing and to assess route dependency of the further pharmacokinetic criteria. To this purpose, point and confidence interval estimates of the true ratio of the treatment mean for sc- relative to iv-dosing will be back-transformed from the ANOVA-derived estimates of the true difference of the treatment means of the log-transformed data. By means of a similar ANOVA, estimates of the differences of the treatment means will be derived for $t_{½}$ and MRT.

Data from Cohort 5 covering the pharmacokinetics after single sc doses of 20, 40 and 60 IU/kg OCTA101 will be used to derive estimates of the dose-proportionality of the pharmacokinetics of FVIII:C and OCTA12. To this purpose, methods as described by Smith et al. (2000) will be used.

Quantifiable and λ_z-extrapolated time courses of the concentrations after single doses (all cohorts) will be used to simulate the time courses when defined doses would be administered

repeatedly at specified interval. To this purpose, the pharmacokinetics will be assumed to be linear i.e. dose-proportional, time-invariant and superimposable. A superposition cascade approach as described by Gibaldi (Biopharmaceutics and Clinical Pharmacokinetics – 4th edition, 1991, Lea & Febinger, Malvern, USA – Appendix II) will be used.

If the smoothness of the time courses of the concentrations permits, estimates of the absorption rate on sc dosing will be derived by the Wagner-Nelson method and/or by compartmental analysis. If appropriate, the time courses of the plasma concentrations will be analysed compartmentally, i.e. fitted to an open mammillary 1-, 2- or 3-compartmental model, and further simulations of the time courses of the concentrations on repeated dosing may be derived.

The total annualized bleeding rate, the spontaneous annualized bleeding rate, the traumatic annualized bleeding rate, the total annualized treated bleeding rate, the spontaneous annualized treated bleeding rate, and the annualized joint bleeding rate during daily sc treatment with OCTA101 will be presented for patients in the FAS and PP set in Cohort 6, grouped by dose level of daily OCTA101 dosing. For the daily dosing period of Cohorts 1 to 3, no bleeding rates were calculated. The observation period was considerably shorter than planned due to the study stop. Bleedings occurred only in patients who had developed antibodies or after the end of the daily dosing period.

All other data collected for BEs, efficacy assessments at the end of BEs will be analyzed descriptively. The proportion of BEs successfully treated with Nuwiq will be presented. Summaries on patient levels will be detailed in the SAP as needed. All data collected will be listed.

FVIII:C and OCTA12 trough and peak plasma levels during daily dosing will be analyzed descriptively.

9.2.3 Safety Analysis Plan

Safety and tolerability data will first be analyzed for each cohort after the first dose(s) and evaluated by an external DMC.

All safety and tolerability parameters (adverse events, vital signs, laboratory monitoring, and physical examination results) will be listed by patient and cohort.

Analyses based on data from repeat dosing from Cohort 1, 2, and 3 with OCTA101 for 3 months will be analyzed separately from data related to the first doses. In these analyses, data will be presented by cohort and overall. Data from single doses after the completion of the repeat dosing will be analyzed separately. All data will be presented together without reference to the original cohort.

Data from Cohort 6 will be analyzed separately and will be split by period (run-in period with Nuwiq and OCTA101 treatment period) and by planned OCTA101 daily dose.

All AEs reported during the study will analyzed and presented. AEs starting at or after the first dose of IMP will be presented separately from those starting prior to the first dose of IMP. For Cohort 6, AEs starting at or after the first dose of Nuwiq and prior to the first dose on OCTA101 will be presented separately from AEs starting after the first dose of OCTA101.

The number and percentage of patients with AEs and the number of AEs will be summarized by primary MedDRA System Organ Class and Preferred Term. Separate tables showing all AEs, all serious AEs and all AEs at least possibly related to IMP will be generated. Further a

summary of AEs by severity, presenting the most severe event per patient overall and within each SOC and PT will be generated.

For thromboembolic events and local injection site reactions, appropriate clusters of MedDRA terms will be defined and such events will be presented within these clusters, using the summaries detailed above.

The frequencies of local injection reactivity ratings by the investigator and the patient (see Section 7.4.1) directly after injection and 15 ± 5 min post-injection will be summarized over the whole daily treatment period using the number of injections as denominator. Further, the worst rating per patient and time period will be summarized. Visual analogue scale assessments of injection site pain will be summarized analogously.

The frequencies (including percentages) of any inhibitor formation to FVIII and antibody formation to OCTA12 will be presented by cohort and overall. Inhibitor formation to FVIII will be considered if at least one result of neutralizing antibody was equal or greater than 0.6 BU/mL. Antibody formation to OCTA12 will be defined as positive if at least one result of OCTA12 antibody was positive at any visit during the study. Results from LumiTope assay will be listed.

Vital sign and safety laboratory parameters will be analyzed using descriptive statistics for measured values and for changes from pre-dose values to each single injection.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed. Any specific rule or convention needed for the statistical analysis to account for possibly missing data will be detailed in the SAP.

9.3 Randomization, Stratification, and Code Release

Not applicable for this open-label study based on sequential cohorts.

9.4 Interim Analysis

After the completion of each cohort, PK and safety data were analyzed and discussed during a DMC meeting. Data from each cohort were analyzed separately. Safety data were compared descriptively and no adjustment of a significance level will be performed. These analyses will also be performed for Cohort 6 for safety and efficacy data.

One separate interim analysis will be performed: this will include all available data of enrolled patients in Cohorts 1, 2, 3, and 5.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and to

the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the eCRF for each patient enrolled.

Each patient will be informed that his medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Coordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names,

but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential subject identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress, whereby monitoring after completion of each cohort is mandatory.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study will be published or presented at scientific meetings.

If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

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15 APPENDICES

a. Appendix 1: Diagram of Subcutaneous Injection Sites

To locate injection sites on the abdomen, use the areas shown in the diagram below, avoiding the belly button, ribs, and hip bones, scars or moles.