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

Summary

EudraCT number	2018-002776-40
Trial protocol	BG
Global end of trial date	18 February 2022

Results information

Result version number	v1 (current)
This version publication date	17 March 2023
First version publication date	17 March 2023

Trial information

Trial identification

Sponsor protocol code	SubQ8-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04046848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, 8853
Public contact	Sigurd Knaub, Octapharma AG, sigurd.knaub@octapharma.com
Scientific contact	Sigurd Knaub, Octapharma AG, sigurd.knaub@octapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP E6 (R2), ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki and with applicable regulatory requirements. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product. For each subject safety was assessed throughout the study duration, such as monitoring of AEs, SAEs and recording of concomitant medication.
Safety data and study progress were reviewed quite frequently by an Independent Data Monitoring Committee. The decision of going to the next higher dose was to 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 von Willebrand Factor fragment dimer. Any safety-relevant signals were also forwarded to the DMC for their review as they occurred.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	35
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male patients aged ≥18 years with severe haemophilia A (<1% FVIII:C) as documented in medical records and having had ≥150 exposure days (EDs) with a FVIII product were screened according to predefined in- and exclusion criteria.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: OCTA101 50 IU/kg sc

Arm description:

Single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing (abdomen or thigh) Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months. Patients received prophylactic Nuwiq for home treatment until the IDMC had confirmed that OCTA101 could be used as daily prophylaxis.
At the end of the 3-month daily prophylactic period PK assessment was performed with 50 IU/kg OCTA101 (abdomen).

Arm type	Experimental
Investigational medicinal product name	OCTA101 (human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose of OCTA101 50 IU/kg sc was administered by sc injection into the abdomen or thigh. Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months.

Arm title	Cohort 2 : OCTA101 100 IU/kg sc

Arm description:

Single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing (abdomen or thigh) followed by a daily prophylactic dosing (40-60 IU/kg) for 3 months. At the end of the 3-month daily prophylactic period PK assessment was to be performed with 50 IU/kg OCTA101 (abdomen).
4 patients completed the initial PK assessment, but only 2 completed the 3-month daily sc treatment period. Only 1 patient completed the repeat PK assessment. The two inhibitor patients as well as one patient whose FVIII levels were very low did not do the repeat PK assessment.

Arm type	Experimental
Investigational medicinal product name	OCTA101 (human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose of OCTA101 100 IU/kg sc was administered by sc injection into the abdomen or thigh.

Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months.

Arm title	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc

Arm description:

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.
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). 8 patients completed the PK assessment but 0 completed the 3-month daily sc treatment period.

Arm type	Experimental
Investigational medicinal product name	OCTA101 (human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose of OCTA101 50 IU/kg sc was administered by sc injection into the abdomen.

Investigational medicinal product name	Nuwiq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc

Arm description:

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 (each in the abdomen).

Arm type	Experimental
Investigational medicinal product name	OCTA101 (human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each patient first received a single dose of 20 IU/kg sc (with 72 hours of observation), followed by a single dose of 40 IU/kg sc (with 72 hours of observation), followed by a single dose of 60 IU/kg sc (with 72 hours of observation) in the abdomen.

Arm title	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily

Arm description:

Following an initial 4-6-week run-in period with Nuwiq iv prophylaxis, 6-month prophylactic treatment with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc, and then depending on the overall data of the first 2 dose levels, 40 IU/kg OCTA101 sc could be considered (exact dosing depends on vial strength). Site of administration (abdomen or thigh) to be chosen by the patient. The study was stopped prematurely during the 12.5 IU/kg OCTA101 sc daily.
16 patients entered the Nuwiq iv run-in and 10 patients went on to receive OCTA101 12.5 IU/kg. The study was terminated before treatment could be completed.

Arm type	Experimental
Investigational medicinal product name	Nuwiq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nuwiq administered for prophylaxis in a 4 to 6-week run-in period.

Investigational medicinal product name	OCTA101 (human-cl rhFVIII and recombinant human von Willebrand Factor fragment dimer)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Planned as 6-month prophylactic treatment with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc, and then depending on the overall data of the first 2 dose levels, 40 IU/kg OCTA101 sc could be considered (exact dosing depends on vial strength). Site of administration (abdomen or thigh) to be chosen by the patient. The study was stopped prematurely during the 12.5 IU/kg.

Number of subjects in period 1	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc
Started	4	4	8
Completed	4	2	0
Not completed	0	2	8
Adverse event, non-fatal	-	-	-
Sponsor decision	-	2	8
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily
Started	4	16
Completed	4	0
Not completed	0	16
Adverse event, non-fatal	-	2
Sponsor decision	-	13
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: OCTA101 50 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing (abdomen or thigh) Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months. Patients received prophylactic Nuwiq for home treatment until the IDMC had confirmed that OCTA101 could be used as daily prophylaxis.
At the end of the 3-month daily prophylactic period PK assessment was performed with 50 IU/kg OCTA101 (abdomen).

Reporting group title	Cohort 2 : OCTA101 100 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing (abdomen or thigh) followed by a daily prophylactic dosing (40-60 IU/kg) for 3 months. At the end of the 3-month daily prophylactic period PK assessment was to be performed with 50 IU/kg OCTA101 (abdomen).
4 patients completed the initial PK assessment, but only 2 completed the 3-month daily sc treatment period. Only 1 patient completed the repeat PK assessment. The two inhibitor patients as well as one patient whose FVIII levels were very low did not do the repeat PK assessment.

Reporting group title	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc

Reporting group description:

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.
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). 8 patients completed the PK assessment but 0 completed the 3-month daily sc treatment period.

Reporting group title	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc

Reporting group description:

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 (each in the abdomen).

Reporting group title	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily

Reporting group description:

Following an initial 4-6-week run-in period with Nuwiq iv prophylaxis, 6-month prophylactic treatment with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc, and then depending on the overall data of the first 2 dose levels, 40 IU/kg OCTA101 sc could be considered (exact dosing depends on vial strength). Site of administration (abdomen or thigh) to be chosen by the patient. The study was stopped prematurely during the 12.5 IU/kg OCTA101 sc daily.
16 patients entered the Nuwiq iv run-in and 10 patients went on to receive OCTA101 12.5 IU/kg. The study was terminated before treatment could be completed.

Reporting group values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc
Number of subjects	4	4	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.0	40.5	43.5
standard deviation	± 7.35	± 11.82	± 12.78

Gender categorical Units: Subjects			
Female	0	0	0
Male	4	4	8

Reporting group values	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily	Total
Number of subjects	4	16	36
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.5	41.9	
standard deviation	± 5.51	± 12.37	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	4	16	36

End points

End points reporting groups

Reporting group title	Cohort 1: OCTA101 50 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing (abdomen or thigh) Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months. Patients received prophylactic Nuwiq for home treatment until the IDMC had confirmed that OCTA101 could be used as daily prophylaxis.
At the end of the 3-month daily prophylactic period PK assessment was performed with 50 IU/kg OCTA101 (abdomen).

Reporting group title	Cohort 2 : OCTA101 100 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing (abdomen or thigh) followed by a daily prophylactic dosing (40-60 IU/kg) for 3 months. At the end of the 3-month daily prophylactic period PK assessment was to be performed with 50 IU/kg OCTA101 (abdomen).
4 patients completed the initial PK assessment, but only 2 completed the 3-month daily sc treatment period. Only 1 patient completed the repeat PK assessment. The two inhibitor patients as well as one patient whose FVIII levels were very low did not do the repeat PK assessment.

Reporting group title	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc

Reporting group description:

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.
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). 8 patients completed the PK assessment but 0 completed the 3-month daily sc treatment period.

Reporting group title	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc

Reporting group description:

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 (each in the abdomen).

Reporting group title	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily

Reporting group description:

Following an initial 4-6-week run-in period with Nuwiq iv prophylaxis, 6-month prophylactic treatment with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc, and then depending on the overall data of the first 2 dose levels, 40 IU/kg OCTA101 sc could be considered (exact dosing depends on vial strength). Site of administration (abdomen or thigh) to be chosen by the patient. The study was stopped prematurely during the 12.5 IU/kg OCTA101 sc daily.
16 patients entered the Nuwiq iv run-in and 10 patients went on to receive OCTA101 12.5 IU/kg. The study was terminated before treatment could be completed.

Subject analysis set title	Safety Analysis (SAF) Cohort 1,2,3,5
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients of Cohorts 1,2,3 and 5 who received at least one dose of IMP.

Subject analysis set title	Safety Analysis (SAF) Cohort 6
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients of Cohort 6 who received at least one dose of IMP.

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

Entire study period after 1st IMP administration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis, data are provided as tables and listings.

End point values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	4
Units: participants	0	2	1	0

End point values	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Primary: Dose-limiting Toxicities (DLTs)

End point title	Dose-limiting Toxicities (DLTs)[2]

End point description:

Pre-defined DLTs for this study were:
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.

End point type	Primary

End point timeframe:

Entire study period after 1st IMP administration

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis, data are provided as tables and listings.

End point values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	4
Units: participants				
number (not applicable)	0	0	0	0

End point values	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Thromboembolic Events

End point title	Thromboembolic Events[3]

End point description:

The definition of the cluster thromboembolic events was based on the standardised MedDRA query (SMQ) "Embolic and thrombotic events":
Definition: Thrombotic disorders are diseases characterized by formation of a thrombus that obstructs vascular blood flow locally or detaches and embolizes to occlude blood flow downstream. Embolism is the sudden blocking of a vessel by a clot or foreign material which has been brought to its site of lodgment by the blood current. (Thrombo-)phlebitis is an inflammation of a vein (phlebitis) associated with thrombus formation (thrombosis).
This SMQ includes 3 sub-SMQ:

- Embolic and thrombotic events, venous (SMQ)
- Embolic and thrombotic events, arterial (SMQ)
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)

End point type	Primary

End point timeframe:

throughout the study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis, data are provided as tables and listings.

End point values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	4
Units: participants				
number (not applicable)	0	0	0	0

End point values	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Local Injection Site Reactions

End point title	Local Injection Site Reactions[4]

End point description:

Investigator (and patient in case of home treatment) did assess local injection reactivity directly after injection and at 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).

End point type	Primary

End point timeframe:

throughout the period where OCTA-101 was injected subcutaneously (sc).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis, data are provided as tables and listings.

End point values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	4
Units: participants				

number (not applicable)	0	1	0	0

End point values	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Inhibitor Formation to FVIII

End point title	Inhibitor Formation to FVIII[5]

End point description:

Inhibitor formation to FVIII was considered if at least one result of neutralizing antibody was equal or greater than 0.6 BU/mL as determined by the central lab.

End point type	Primary

End point timeframe:

From first injection to 4 months after start of of daily injection (cohorts 1, 2 and 3), 4 weeks after last PK injection (cohort 5), monthly during the daily sc treatment period (cohort 6)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis, data are provided as tables and listings.

End point values	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc	Cohort 5: OCTA101 20, 40 and 60 IU/kg sc
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	4
Units: participants				
number (not applicable)	0	2	1	0

End point values	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				

number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire study period after 1st IMP administration

Adverse event reporting additional description:

Data from repeat dosing were analysed separately from data related to the first doses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Cohort 1: OCTA101 50 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 50 IU/kg OCTA101 profiled up to 72 hours after dosing (abdomen or thigh) Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months.
At the end of the 3-month daily prophylactic period PK assessment was to be performed with 50 IU/kg OCTA101 (abdomen).

Reporting group title	Cohort 2 : OCTA101 100 IU/kg sc

Reporting group description:

Single-period investigation with a single sc dose of 100 IU/kg OCTA101 profiled up to 96 hours after dosing. (abdomrn of tigh) Following review of safety and tolerability data by Data Monitoring Committee a daily prophylactic dosing (40-60 IU/kg) for 3 months. At the end of the 3-month daily prophylactic period PK assessment was to be performed with 50 IU/kg OCTA101 (abdomen).

4 patients completed the PK assessment, but only 2 completed the 3-month daily sc treatment period as the DMC recommended cessation of all current and planned dosing of OCTA101 for any reason

Reporting group title	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc

Reporting group description:

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. Following review of safety and tolerability data by Data Monitoring Committee daily prophylactic dosing (40-60 IU/kg) for 3 months

8 patients completed the PK assessment but 0 completed the 3-month daily sc treatment period as the DMC recommended cessation of all current and planned dosing of OCTA101 for any reason

Reporting group title	Cohort 5: OCTA101 20 , 40 and 60 IU/kg sc

Reporting group description:

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 (each in the abdomen). 4 patients completed the PK assessment, but were not assigned to treatment as the DMC recommended cessation of all current and planned dosing of OCTA101 for any reason.

Reporting group title	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily

Reporting group description:

Planned as 6-month prophylactic treatment with 12.5 IU/kg OCTA101 sc daily, then 25 IU/kg OCTA101 sc, and then depending on the overall data of the first 2 dose levels, 40 IU/kg OCTA101 sc could be considered (exact dosing depends on vial strength). Site of administration (abdomen or thigh) to be chosen by the patient. The study was stopped prematurely during the 12.5 IU/kg OCTA101 sc daily 16 patients entered the Nuwiq iv run-in and 10 patients went on to receive OCTA101 12.5 IU/kg. The study was terminated before treatment could be completed.

Serious adverse events	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Spontaneous haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Hemoperitoneum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 5: OCTA101 20 , 40 and 60 IU/kg sc	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Anti factor VIII antibody positive			

subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Spontaneous haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hemoperitoneum			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1: OCTA101 50 IU/kg sc	Cohort 2 : OCTA101 100 IU/kg sc	Cohort 3: Nuwiq 50 IU/kg iv followed by OCTA101 50 IU/kg sc
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
Investigations			
Roseolovirus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 8 (0.00%) 0
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 8 (0.00%) 0

Non-serious adverse events	Cohort 5: OCTA101 20 , 40 and 60 IU/kg sc	Cohort 6: Nuwiq iv prophylaxis, OCTA101 sc daily	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	
Investigations Roseolovirus test positive subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 16 (0.00%) 0	
Injury, poisoning and procedural complications Road traffic accident subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 16 (0.00%) 0	
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 16 (6.25%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2019	Amendment 1 • The study timelines were updated. • It was clarified that only 1 study centre will be required. • It was clarified that the molar ratio of 1:6 FVIII to OCTA12 is with regards to the binding sites in OCTA12. • An additional PK assessment was added in all patients from Cohorts 1 and 2 who completed their 3-month daily injection period further characterizing the PK of FVIII:C and OCTA12. • Clarification of the use of vials to achieve targeted doses. • Clarification that haemophilia joint health score (HJHS) was to be assessed at screening. • Final physical examination in Cohorts 1 and 2 moved to end of additional PK assessment. • Time windows for additional PK assessment in Cohorts 1 and 2 added. • Change of address for central laboratory assessing anti-OCTA12.
19 November 2019	Amendment 2 • 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 the 50 IU/kg dose was instead warranted. The study design was modified accordingly. Cohort 4 was cancelled. • The benefit-risk statement was updated to reflect the observation of an inhibitor in Cohort 2 and the revised study design. The stopping rules were also revised. • It was clarified that the full content of vials does not have to be injected.
28 April 2020	Amendment 3 • The study design was adapted based on the observation of inhibitor formation in Cohort 2, with the introduction of another cohort, Cohort 6. In Cohort 6, 12.5 IU/kg OCTA101, then 25 IU/kg OCTA101, and then 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 protocol was updated to reflect the status of the study at the time of amendment 3 and a summary of findings from Cohorts 1, 2, 3 and 5 was added. • The benefit-risk statement was updated to reflect the observation of an inhibitor in Cohort 2 and the revised study design. The stopping rules were also revised. • A new exclusion criterion was added: "For Cohort 6, patients with a positive LumiTope test at screening will be excluded." • Home visits by a study nurse were planned for Cohort 6. • Given the revised study design, the estimated date for the clinical end of the study was updated.
06 July 2020	Amendment 4 • At the request of the Bulgarian Drug Agency, there will be no home visits by a study nurse in Cohort 6. • The IND for this product was withdrawn so the IND number was removed from the protocol. • The test base for inhibitor determination was clarified. • The method for determining positive/negative LumiTope assay results was added.
03 March 2021	Amended Protocol version 08 Cohort 6 revised to: around 18 – 20 patients (to compensate for possible early drop-outs) will 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.

30 July 2021	Amended Protocol version 09 It was decided to stop all further treatment with OCTA101, but to offer all enrolled patients access to Nuwiq prophylactic treatment until they were integrated into the National Health Insurance program for haemophilia A patients, again, but no longer than until the end of September 2021 + 2 week time window.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 December 2019	The DMC put the study on hold on 02-Dec-2019 as two patients of cohort 2 had developed an inhibitor to FVIII. As a consequence, patients of cohort 3 terminated the IMP treatment prematurely while patients of cohorts 1, 2 and 5 had already completed IMP study treatment at this time (there were no cohort 4 patients). Later on, the study continued with a revised protocol with a new cohort (cohort 6).	07 October 2020

Notes:

Limitations and caveats

None reported