Clinical trial results:
Evaluation of safety following Immune Tolerance Induction treatment with turoctocog alfa in patients with haemophilia A following inhibitor development in NN7170-4213 trial

Summary

EudraCT number	2016-003821-40
Trial protocol	GB AT BG DE
Global end of trial date	19 June 2019

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019

Trial information

Trial identification

Sponsor protocol code	NN7170-4345

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03588741
WHO universal trial number (UTN)	U1111-1187-7323

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.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	31 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2019
Global end of trial reached?	Yes
Global end of trial date	19 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety of immune tolerance induction treatment with turoctocog alfa in patients who have developed neutralising antibodies against coagulation factor VIII (FVIII) after exposure to subcutaneous turoctocog alfa pegol during participation in NN7170-4213.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (October 2013), ICH Good Clinical Practice, including archiving of essential documents (June 1996), and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	12 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	1
EEA total number of subjects	1

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)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 1 trial site in Germany.

Pre-assignment

Screening details:

Previously treated subjects with severe haemophilia A (FVIII activity <1% according to medical records) who had developed clinically relevant FVIII inhibitors in trial NN7170-4213 were offered immune tolerance induction (ITI) treatment with turoctocog alfa.

Period 1

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

Arms

Arm title	Turoctocog alfa

Arm description:

The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week.

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

Dosage and administration details:

The subject received i.v. injection of 65 IU/kg turoctocog alfa 3 times per week. The total consumption of turoctocog alfa comprised of a total of 8 administrations of between 63 and 65 IU/kg each.

Number of subjects in period 1	Turoctocog alfa
Started	1
Completed	0
Not completed	1
Withdrawal by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Turoctocog alfa
Reporting group description:	
The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week.	

Reporting group values	Turoctocog alfa	Total	
Number of subjects	1	1	
Age Categorical Units: Subjects			
Adults (18-64 years)	1	1	
Age Continuous			
Since the study enrolled a single subject, the age continuous data is not provided as this could be against General Data Protection Regulation (EU) 2016/679 (GDPR).			
Units: years arithmetic mean standard deviation	 0 ± 0	 -	
Gender Categorical Units: Subjects			
Male	1	1	

End points

End points reporting groups

Reporting group title	Turoctocog alfa

Reporting group description:

The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set (FAS) comprised of all subjects who initiated ITI treatment with turoctocog alfa.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set (SAS) comprised of all subjects who initiated ITI treatment with turoctocog alfa.

Primary: Number of adverse events

End point title	Number of adverse events[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. SAS comprised of all subjects who initiated ITI treatment with turoctocog alfa.

End point type	Primary

End point timeframe:

During immune tolerance induction treatment with turoctocog alfa.

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: The primary endpoint investigated safety and was analysed using descriptive statistics, and thus no statistical analysis was performed.

End point values	Turoctocog alfa			
Subject group type	Reporting group			
Number of subjects analysed	1[2]			
Units: Events	6			

Notes:

[2] - SAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Response to immune tolerance induction treatment (success, partial success, failure, other)

End point title	Response to immune tolerance induction treatment (success, partial success, failure, other)

End point description:

ITI treatment response was categorized as: 1. Success: Undetectable inhibitor titre <0.6 bethesda units (BU) (or lower limit of quantification [LLoQ] if above 0.6 BU); Normalised FVIII in vivo recovery, defined as ≥0.013 international units (IU) per milliliter per IU per kilogram ((IU/ml)/(IU/kg)) (66% of expected incremental recovery); turoctocog alfa half-life ≥7 hours (based on FVIII activity) after 72 hours treatment-free washout period. 2. Partial success: Inhibitor titre ≤5 BU; Clinical effect of turoctocog alfa therapy as judged by the investigator. 3. Failure (one criterion had to be fulfilled): Failure to attain

defined success or partial success after 24 months of ITI treatment with turoctocog alfa; Decrease in inhibitor titre after 12 months of ITI treatment <20% compared to peak titre. 4. Other: Subjects not fulfilling the above criteria e.g. early withdrawal from ITI treatment, lack of adherence to recommended ITI protocol etc. FAS.

End point type	Secondary

End point timeframe:

Within a maximum immune tolerance induction treatment duration of 24 months.

End point values	Turoctocog alfa			
Subject group type	Reporting group			
Number of subjects analysed	1[3]			
Units: Subjects				
Success	0			
Partial success	0			
Failure	0			
Other	1			

Notes:

[3] - FAS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 31 months

Adverse event reporting additional description:

Evaluation of safety was based on SAS which comprised of all subjects who initiated ITI treatment with turoctocog alfa.

'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events'.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Turoctocog alfa

Reporting group description:

Subjects received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week. The total consumption of turoctocog alfa comprised of a total of 8 administrations of between 63 and 65 IU/kg each.

Serious adverse events	Turoctocog alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Turoctocog alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle disorder			

subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 1 (100.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2019	1) To align with new internal procedures in Novo Nordisk. Summary of Product Characteristics will no longer be the source of the Reference Safety Information (RSI) for assessment of AE expectedness. 2) Change in treatment of patient section, in order to allow investigators to treat the patients as deemed relevant and according to local guidelines. 3) Testing for non-neutralising antibodies will only be performed if deemed relevant or for safety reasons, e.g. in case of adverse events suspected of being related to antibodies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported