Clinical trial results:
Safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated patients with moderate or severe haemophilia A in India

Summary

EudraCT number	2017-002281-46
Trial protocol	Outside EU/EEA
Global end of trial date	22 April 2019

Results information

Result version number	v1 (current)
This version publication date	25 October 2019
First version publication date	25 October 2019

Trial information

Trial identification

Sponsor protocol code	NN7008-4304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03449342
WHO universal trial number (UTN)	U1111-1179-5950

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, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2019
Global end of trial reached?	Yes
Global end of trial date	22 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety of turoctocog alfa during treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe haemophilia A in India

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	23 February 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	India: 60
Worldwide total number of subjects	60
EEA total number of subjects	0

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)	10
Adults (18-64 years)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 10 sites in India.

Pre-assignment

Screening details:

A washout period for a minimum of 72 hours for factor 8 (FVIII) containing products prior to collection of FVIII activity and FVIII inhibitor laboratory samples at visit 1 (screening) was done to ensure subject eligibility. Prior to visit 4 (end of trial), a washout of minimum 48 hours was done to avoid interference with the FVIII inhibitor assay

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Adolescents (12 - <18 years)

Arm description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

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:

Dosing for prophylaxis was according to the approved prescribing information. The recommended frequency of dosing could be either every second day or 3 times weekly, at a dose in the range of 20-50 IU/kg. Bleeds were treated with one or more turoctocog alfa intravenous (i.v.) bolus injections. The individual dose levels were decided by the investigator based on recommendations from the World Federation of Hemophilia (WFH). Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL.

Arm title	Adults (≥18 years)

Arm description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

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:

Dosing for prophylaxis was according to the approved prescribing information. The recommended

frequency of dosing could be either every second day or 3 times weekly, at a dose in the range of 20-50 IU/kg. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL.

Number of subjects in period 1	Adolescents (12 - <18 years)	Adults (≥18 years)
Started	10	50
Completed	10	50

Baseline characteristics

Reporting groups	
Reporting group title	Adolescents (12 - <18 years)
Reporting group description:	
Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.	
Reporting group title	Adults (≥18 years)
Reporting group description:	
Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.	

Reporting group values	Adolescents (12 - <18 years)	Adults (≥18 years)	Total
Number of subjects	10	50	60
Age Categorical Units: Subjects			
Adolescents (12-17 years)	10	0	10
Adults (18-64 years)	0	50	50
Age Continuous Units: years			
arithmetic mean	13.90	27.10	
standard deviation	± 1.91	± 7.28	-
Gender Categorical Units: Subjects			
Male	10	50	60

End points

End points reporting groups

Reporting group title	Adolescents (12 - <18 years)

Reporting group description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

Reporting group title	Adults (≥18 years)

Reporting group description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

Primary: Occurrence of confirmed FVIII inhibitor development (≥ 0.6 BU)

End point title	Occurrence of confirmed FVIII inhibitor development (≥ 0.6 BU)[1]

End point description:

The number of participants who confirmed the presence of FVIII inhibitor development (≥ 0.6 BU) during the trial. Results are based on the full analysis set (FAS), that included all dosed participants with data after dosing during 8 weeks of treatment.

End point type	Primary

End point timeframe:

During 8 weeks of treatment

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	Adolescents (12 - <18 years)	Adults (≥18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	50		
Units: Participants				
Number of subjects with inhibitor antibodies	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of adverse drug reactions (AR) and serious adverse reactions (SAR)

End point title	Frequency of adverse drug reactions (AR) and serious adverse reactions (SAR)

End point description:

Frequency of adverse drug reactions (ARs) and serious adverse reactions (SARs) are presented as rate of events, which was calculated as the number of ARs per patient years. All presented ARs and SARs are treatment emergent and related to trial product, which were defined as the events reported after trial

product administration until the follow-up, 12 weeks after first treatment. Results are based on the safety analysis set, that included all dosed participants with data after dosing during 8 weeks of treatment.

End point type	Secondary

End point timeframe:

Reported until follow-up, 12 weeks after first treatment

End point values	Adolescents (12 - <18 years)	Adults (≥18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	50		
Units: Rate of reactions				
number (not applicable)				
Adverse drug reactions	0	0		
Serious adverse reactions	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Successful haemostatic effect of turoctocog alfa in the treatment of bleeding episodes

End point title	Successful haemostatic effect of turoctocog alfa in the treatment of bleeding episodes

End point description:

The haemostatic effect of turoctocog alfa when used for treatment of bleeding episodes was evaluated during 8 weeks of treatment. Results are based on the FAS that included all dosed participants with data after dosing during 8 weeks of treatment.

End point type	Secondary

End point timeframe:

During 8 weeks of treatment

End point values	Adolescents (12 - <18 years)	Adults (≥18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[2]	46[3]		
Units: % of bleeding episodes				
number (not applicable)	66.7	82.6		

Notes:

[2] - Number of subjects analysed = number of bleeding episodes treated with turoctocog alfa

[3] - Number of subjects analysed = number of bleeding episodes treated with turoctocog alfa

Statistical analyses

No statistical analyses for this end point

Secondary: Total annualised consumption of turoctocog alfa

End point title	Total annualised consumption of turoctocog alfa

End point description:

Total consumption of turoctocog alfa (IU/kg body weight (BW) per year) per participant was evaluated during 8 weeks of treatment. Results are based on the FAS that included all dosed participants with data after dosing during 8 weeks of treatment.

End point type	Secondary

End point timeframe:

Measured during the 8 weeks of treatment

End point values	Adolescents (12 - <18 years)	Adults (≥18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	50		
Units: IU/kg BW/year/participant				
arithmetic mean (standard deviation)	7030 (± 1053)	6086 (± 1735)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of allergic or infusion reactions related to the trial product

End point title	Frequency of allergic or infusion reactions related to the trial product

End point description:

Frequency of allergic or infusion reactions related to trial products are presented as rate of adverse reactions, which was calculated as the number of reactions per patient years. Allergic reactions are a class of adverse events related to allergy. Results are based on the safety analysis set, that included all dosed participants with data after dosing during 8 weeks of treatment.

End point type	Secondary

End point timeframe:

Reported until follow-up, 12 weeks after first treatment

End point values	Adolescents (12 - <18 years)	Adults (≥18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	50		
Units: Rate of adverse reactions				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 - 12 (8 weeks of treatment period + 4 weeks of follow-up period).

Adverse event reporting additional description:

All the adverse events are based on the SAS which included all dosed participants with data after dosing. '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	21

Reporting groups

Reporting group title	Adolescents (12 - <18 years)

Reporting group description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

Reporting group title	Adults (≥18 years)

Reporting group description:

Participants were to receive preventive turoctocog alfa at a frequency of 'every second day' or '3 times a week' at a dose in the range of 20-50 IU/kg at the investigator's discretion. The total treatment duration for each participant was 8 weeks.

Serious adverse events	Adolescents (12 - <18 years)	Adults (≥18 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 50 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adolescents (12 - <18 years)	Adults (≥18 years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	2 / 50 (4.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	2 / 50 (4.00%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported