Clinical trial results:
Efficacy and Safety of NNC 0129-0000-1003 (N8-GP) during Surgical Procedures in Patients with Haemophilia A

Summary

EudraCT number	2011-001144-30
Trial protocol	NL DE SE DK GB ES HU IT BG
Global end of trial date	10 December 2018

Results information

Result version number	v1 (current)
This version publication date	22 June 2019
First version publication date	22 June 2019

Trial information

Trial identification

Sponsor protocol code	NN7088-3860

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01489111
WHO universal trial number (UTN)	U1111-1119-7326
Other trial identifiers	Japanese trial registration number: 132215

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001174-PIP02-12
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	21 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2018
Global end of trial reached?	Yes
Global end of trial date	10 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the haemostatic effect of N8-GP during surgical procedures in patients with haemophilia A

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, October 2008), ICH Good Clinical Practice, including archiving of essential documents (Geneva, May 1996), and 21 CFR 312.120.

Background therapy:

Subjects were transferred from the pivotal trial (NN7088-3859), in which patients at inclusion were required to be with a documented history of at least 150 exposure days to other FVIII products.

Evidence for comparator:

Not applicable

Actual start date of recruitment	03 August 2012
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	Australia: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	53
EEA total number of subjects	29

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)	1
Adults (18-64 years)	49
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 26 sites in 13 countries, as follows: Australia (1 site), Denmark (1 site), France (3 sites), Hungary (1 site), Israel (1 site), Italy (2 sites), Japan (2 sites), Malaysia (1 site), Netherlands (1 site), Switzerland (2 sites), Turkey (3 sites), United Kingdom (4 sites) and United States (4 sites).

Pre-assignment

Screening details:

In this trial 36 subjects were exposed and all the results are analysed and presented based on surgery level (number of planned surgeries=53).

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	N8-GP

Arm description:

Subjects (from trial NN7088-3859) undergoing major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The total duration of the trial was 2-5 weeks. Upon completion of this trial, subjects returned to trial NN7088-3859.

Arm type	Experimental
Investigational medicinal product name	N8-GP rFVIII
Investigational medicinal product code	
Other name	ESPEROCT®
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The trial product was administered as a slow bolus intravenous injection. The administrations were performed both at home and in hospital. Dosing was done at the investigators' discretion (except a fixed dose of 50 IU/kg at screening visit). The dose level of N8-GP during this trial was chosen following the coagulation factor 8 (FVIII) activity levels recommended by World Federation of Hemophilia (WFH) guidelines. Higher levels could be necessary depending on type of surgery and standard practice at site. The WFH guidelines for desired FVIII levels in major surgery are as follows: pre-surgery (day 0): 80−100%; post-surgery days 1−3: 60−80%; days 4−6: 40−60%; days 7−14: 30−50%. For treatment of a bleeding episode, all subjects were treated with doses between 20−75 IU/kg. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg.

Number of subjects in period 1	N8-GP
Started	53
Completed	49
Not completed	4
Withdrawal criterion	4

Baseline characteristics

Reporting groups	
Reporting group title	N8-GP

Reporting group description:

Subjects (from trial NN7088-3859) undergoing major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The total duration of the trial was 2-5 weeks. Upon completion of this trial, subjects returned to trial NN7088-3859.

Reporting group values	N8-GP	Total	
Number of subjects	53	53	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	49	49	
From 65-84 years	3	3	
Age Continuous Units: years			
arithmetic mean	40.6		
standard deviation	± 13.1	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	53	53	

End points

End points reporting groups

Reporting group title	N8-GP

Reporting group description:

Subjects (from trial NN7088-3859) undergoing major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The total duration of the trial was 2-5 weeks. Upon completion of this trial, subjects returned to trial NN7088-3859.

Subject analysis set title	N8-GP (completed surgeries)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (from trial NN7088-3859) who completed major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The total duration of the trial was 2-5 weeks. Upon completion of this trial, patients returned to trial NN7088-3859.

Primary: Haemostatic effect during surgery evaluated by the four-point scale, assessed by the Investigator/surgeon at the day of surgery - Four-point response scale: excellent, good, moderate or none

End point title	Haemostatic effect during surgery evaluated by the four-point scale, assessed by the Investigator/surgeon at the day of surgery - Four-point response scale: excellent, good, moderate or none[1]

End point description:

Haemostatic effect during surgery was evaluated on a four-point response scale as 'none', 'moderate', 'good' and 'excellent'. This was assessed after completion of surgery (defined as "last stitch").
Excellent: Better than expected/predicted in this type of procedure.
Good: As expected in this type of procedure.
Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen.
None: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required.
Analysis population: Full analysis set included all subjects exposed to the trial drug (N8-GP) and completed surgeries.

End point type	Primary

End point timeframe:

During surgery

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: As the study includes only one arm, no statistical analysis is performed. All endpoints are summarised.

End point values	N8-GP (completed surgeries)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: number of surgeries				
Excellent	25			
Good	22			
Moderate	2			
None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Average consumption of N8-GP during surgery

End point title	Average consumption of N8-GP during surgery

End point description:

Average consumption of N8-GP, during surgery is presented. The time during surgery is defined from 'knife to skin' until 'last stitch'. Analysis population: Full analysis set included all subjects exposed to the trial drug (N8-GP) and completed surgeries.

End point type	Secondary

End point timeframe:

The endpoint was analysed based on all available information until End of Trial (EOT) Visit and up to approximately 5 weeks for each patient.

End point values	N8-GP (completed surgeries)			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: IU/kg				
arithmetic mean (standard deviation)	20.7 (± 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP during the post-operative period Days 1-6 and 7-14

End point title	Haemostatic effect of N8-GP during the post-operative period Days 1-6 and 7-14

End point description:

Haemostatic effect during post-operative period Days 1-6 and 7-14 was evaluated on a four-point response scale as 'none', 'moderate', 'good' and 'excellent'.
Excellent: Better than expected/predicted in this type of procedure.
Good: As expected in this type of procedure.
Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen.
None: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required. Analysis population: Full analysis set included all subjects exposed to the trial drug (N8-GP).

End point type	Secondary

End point timeframe:

The endpoint was analysed based on all available information until End of Trial (EOT) Visit and up to approximately 5 weeks for each patient.

End point values	N8-GP (completed surgeries)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: number of surgeries				
Day-1-6: Excellent	0			
Day-1-6: Good	1			
Day-1-6: Moderate	0			
Day-1-6: None	0			
Day-1-6: Missing	1			
Day-7-14: Excellent	1			
Day-7-14: Good	1			
Day-7-14: Moderate	0			
Day-7-14: None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Average consumption of N8-GP during the post-operative period Days 1-6

End point title	Average consumption of N8-GP during the post-operative period Days 1-6

End point description:

Average consumption of N8-GP during post operative period days 1-6 is presented. Analysis population: Full analysis set included all subjects exposed to the trial drug (N8-GP) and completed surgery.

End point type	Secondary

End point timeframe:

The endpoint was analysed based on all available information until End of Trial (EOT) Visit and up to approximately 5 weeks for each patient.

End point values	N8-GP (completed surgeries)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: IU/kg				
arithmetic mean (standard deviation)	33.0 (± 10.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of inhibitors against factor VIII (FVIII) (≥0.6 BU/mL)

End point title	Incidence rate of inhibitors against factor VIII (FVIII) (≥0.6

	BU/mL)

End point description:

Incidence rate of inhibitors is the number of newly developed inhibitors per surgery. Development of FVIII inhibitors was measured by a validated Nijmegen modified Bethesda assay. A positive inhibitor test was defined as ≥0.6 bethesda unit. Number of surgeries with inhibitors at the end of trial is presented. Analysis population: safety analysis set (SAS) included all patients exposed to trial drug (N8-GP).

End point type	Secondary

End point timeframe:

The endpoint was analysed based on all available information until End of Trial (EOT) Visit and up to approximately 5 weeks for each patient.

End point values	N8-GP (completed surgeries)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: number of surgeries	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial related activity (day 0) after the patient has signed the informed consent until the end of trial (earliest at day 14).

Adverse event reporting additional description:

Adverse events were reported for the safety analysis set (SAS) which includes all subjects exposed to trial drug (N8-GP). The number of subjects refers to the number of surgeries.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	N8-GP

Reporting group description:

Subjects (from trial NN7088-3859) undergoing major surgery received bleeding preventive treatment with N8-GP before, during and after surgery. The total duration of the trial was 2-5 weeks. Upon completion of this trial, subjects returned to trial NN7088-3859.

Serious adverse events	N8-GP		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 53 (7.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Pancreatitis acute			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	N8-GP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 53 (56.60%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
C-reactive protein increased			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Haemoglobin decreased			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Procedural pain			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 4		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 11 / 53 (20.75%) 11 3 / 53 (5.66%) 3 6 / 53 (11.32%) 6 3 / 53 (5.66%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2011	Amendment was issued primarily as a response to a Voluntary Harmonised Procedure (VHP) assessment. Minor adjustment to the protocol have been made. Also changes to the Subject Information/Informed Consent are reflected in this amendment
13 April 2012	This protocol amendment was issued primarily to change the requirement for the timing of the pre-operative loading dose and secondarily to align with the NN7088-3859 (pathfinderTM2) substantial protocol amendment issued simultaneously. In conjunction other minor clarifications to the protocol has also been included.
21 January 2014	1. Addition of a trial site 2. Decision that the present trial would remain open to ensure that subjects participating in the NN7088-3859 trial (including extension parts) would have the opportunity to undergo major surgery. Thus, patients would be offered to continue on N8-GP until commercially available ensuring that they could undergo surgery without having to switch product. 3. Withdrawal criteria was amended to allow subjects with a low titre inhibitor (≤5 BU), that did not result in clinically ineffective treatment with N8-GP, to continue in the trial. 4. Minor surgery definitions aligned with trial NN7088-3859. 5. Israel added to country list. 6. Text updated to reflect what the subject had consented to regarding storage of samples (if allowed by local law). 7. Responsibilities regarding labelling and packing of trial product were updated. 8. Text regarding serious adverse events was specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28470862