



Clinical trial results:

Paradigm 6: Safety and Efficacy of nonacog beta pegol (N9-GP) in Previously Untreated Patients with Haemophilia B - An Open-label Single-arm Multicentre Non-controlled Phase 3a Trial Investigating Safety and Efficacy of Nonacog Beta Pegol (N9-GP) in Prophylaxis and Treatment of Bleeding Episodes in Previously Untreated Patients With Haemophilia B (FIX Activity Below or Equal to 2 Percent)

Summary

EudraCT number	2012-004867-38
Trial protocol	DE AT ES RO IT
Global end of trial date	27 October 2022

Results information

Result version number	v1 (current)
This version publication date	12 May 2023
First version publication date	12 May 2023

Trial information

Trial identification

Sponsor protocol code	NN7999-3895
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141074
WHO universal trial number (UTN)	U1111-1135-9557

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), 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)	EMA-000731-PIP01-09
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	08 December 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate immunogenicity of N9-GP (nonacog beta pegol)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki 2010 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents 1996 and United States Food and Drug Administration (FDA) 21 US Code of Federal Regulations (CFR) 312, 50, and 56 2013.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
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	Austria: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	54
EEA total number of subjects	6

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	5
Infants and toddlers (28 days-23 months)	40
Children (2-11 years)	9
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 29 sites in 11 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): Australia (1/1), Austria (2/2), Canada (1/1), Israel (1/1), Japan (1/1), Malaysia (4/4), Spain (3/3), Taiwan (2/2), Thailand (2/2), United Kingdom (3/3), United States (9/9).

Pre-assignment

Screening details:

Trial consists of main phase including pre-prophylaxis & prophylaxis, extension phase & prophylaxis period until end of treatment. Pre-prophylaxis was optional and allowed subjects to receive treatment until 24 months of age/upon reaching 20EDs, whichever came first. Other subjects directly started on prophylaxis treatment at visit 1.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Pre-prophylaxis

Arm description:

Subjects received nonacog beta pegol 40 international units/kilogram (IU/kg) intravenous injection at intervals longer than a week on-demand for bleeding episodes until they were 24 months of age or until 20 exposure days (ED), whichever came first, in the main phase. Subjects switched from pre-prophylaxis treatment to prophylaxis treatment no later than 24 months of age/20 ED, whichever came first.

Arm type	Experimental
Investigational medicinal product name	Nonacog beta pegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nonacog beta pegol 40 IU/kg intravenous injection at intervals longer than a week until subjects were 24 months of age or until 20 exposure days (ED), whichever came first in the main phase.

Arm title	Prophylaxis
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Arm description:

Subjects who started with pre-prophylaxis were switched to prophylaxis no later than 24 months of age or upon reaching 20EDs, whichever came first. Other subjects who started directly on prophylaxis since visit 1 received once weekly dosing of nonacog beta pegol 40 IU/kg intravenous injection in the main phase, extension phase, and until the end of treatment.

Arm type	Experimental
Investigational medicinal product name	Nonacog beta pegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nonacog beta pegol 40 IU/kg intravenous injection once weekly in the main phase, extension phase and until the end of treatment.

Number of subjects in period 1	Pre-prophylaxis	Prophylaxis
Started	34	51
Completed	31	41
Not completed	3	10
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	4
Other	-	3
Withdrawal by parent/guardian	-	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Subjects received pre-prophylaxis treatment of nonacog beta pegol 40 IU/kg intravenous injection at intervals longer than a week on-demand for bleeding episodes until they were 24 months of age or until 20 exposure days (ED) whichever came first in the main phase. After which they switched to prophylaxis treatment. In prophylaxis, subjects received nonacog beta pegol 40 IU/kg intravenous injection once weekly in the main phase, extension phase and until end of treatment.

Reporting group values	Overall Study	Total	
Number of subjects	54	54	
Age Categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	5	5	
Infants and toddlers (28 days-23 months)	40	40	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	0.8		
standard deviation	± 1.1	-	
Gender Categorical			
Units: Subjects			
Female	0	0	
Male	54	54	

End points

End points reporting groups

Reporting group title	Pre-prophylaxis
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Reporting group description:

Subjects received nonacog beta pegol 40 international units/kilogram (IU/kg) intravenous injection at intervals longer than a week on-demand for bleeding episodes until they were 24 months of age or until 20 exposure days (ED), whichever came first, in the main phase. Subjects switched from pre-prophylaxis treatment to prophylaxis treatment no later than 24 months of age/20 ED, whichever came first.

Reporting group title	Prophylaxis
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Reporting group description:

Subjects who started with pre-prophylaxis were switched to prophylaxis no later than 24 months of age or upon reaching 20EDs, whichever came first. Other subjects who started directly on prophylaxis since visit 1 received once weekly dosing of nonacog beta pegol 40 IU/kg intravenous injection in the main phase, extension phase, and until the end of treatment.

Primary: Incidence of Inhibitory Antibodies Against Coagulation Factor IX (FIX) (50 Exposure Days)

End point title	Incidence of Inhibitory Antibodies Against Coagulation Factor IX (FIX) (50 Exposure Days) ^[1]
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End point description:

Incidence of inhibitory antibodies against FIX after 50 ED is presented. Incidence of inhibitory antibodies against FIX was defined as an inhibitory antibody titre greater than equal to 0.6 Bethesda unit (BU) at two consecutive tests performed at the central laboratory and also tested positive for nonacog beta pegol binding antibodies. Safety analysis set included all subjects exposed to nonacog beta pegol. Number of Subjects Analysed = Subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

When minimum 20 previously untreated patients (PUPs) have reached at least 50 exposure days (ED)

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 comparative statistical analysis was performed between the reported groups.

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	28		
Units: Subjects	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Inhibitory Antibodies Against FIX (100 ED)

End point title	Incidence of Inhibitory Antibodies Against FIX (100 ED) ^[2]
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End point description:

Incidence of inhibitory antibodies against FIX after 100 ED is presented. Incidence of inhibitory antibodies against FIX was defined as an inhibitory antibody titre greater than equal to 0.6 Bethesda unit (BU) at two consecutive tests performed at the central laboratory and also tested positive for

nonacog beta pegol binding antibodies. Safety analysis set included all subjects exposed to nonacog beta pegol. Number of Subjects Analysed = Subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

When minimum 40 PUPs have reached at least 100 ED

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 comparative statistical analysis was performed between the reported groups.

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	47		
Units: Subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Inhibitory Antibodies Against FIX (At End of Trial)

End point title	Incidence of Inhibitory Antibodies Against FIX (At End of
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End point description:

Incidence of inhibitory antibodies against FIX at end of trial is presented. Incidence of inhibitory antibodies against FIX was defined as an inhibitory antibody titre greater than equal to 0.6 Bethesda unit (BU) at two consecutive tests performed at the central laboratory and also tested positive for nonacog beta pegol binding antibodies. Safety analysis set included all subjects exposed to nonacog beta pegol. Number of Subjects Analysed = Subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

At end of trial

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 comparative statistical analysis was performed between the reported groups.

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	51		
Units: Subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adverse Events

End point title	Number of Adverse Events
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End point description:

Number of adverse events after 50 ED, after 100 ED, and at end of trial is presented. An adverse event

was defined as any untoward medical occurrence in a subject who was administered a product, and which does not necessarily have a causal relationship with this treatment. All presented adverse events are treatment emergent adverse events, defined as an event that occurred while the subject was on treatment in the period from first dosing with nonacog beta pegol to the end of trial/discontinuation of treatment. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events				
number (not applicable)				
50 ED (n=24,28)	86	291		
100 ED (n=32,47)	131	610		
End of trial (n=34,51)	134	794		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events

End point title	Frequency of Adverse Events
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End point description:

Frequency of adverse events after 50 ED, after 100 ED, and at end of trial is presented. An adverse event was defined as any untoward medical occurrence in a subject who was administered a product, and which does not necessarily have a causal relationship with this treatment. All presented adverse events are treatment emergent adverse events, defined as an event that occurred while the subject was on treatment in the period from first dosing with nonacog beta pegol to the end of trial/discontinuation of treatment. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events per patient years of exposure				
number (not applicable)				
50 ED (n=24,28)	5.59	5.87		
100 ED (n=32,47)	5.92	5.08		

End of trial (n=34,51)	5.52	4.10		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of Serious Adverse Events

End point title	Number of Serious Adverse Events
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End point description:

Number of serious adverse events after 50 ED, after 100 ED, and at end of trial is presented. A serious adverse event was an experience that at any dose resulted in: death; life-threatening experience; in-patient hospitalisation or prolongation of existing hospitalisation; a persistent or significant disability/incapacity; congenital anomaly/birth defect; important medical events that may not result in death, be life-threatening/require hospitalisation could be considered a serious adverse event based upon appropriate medical judgement. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events				
number (not applicable)				
50 ED (n=24,28)	9	14		
100 ED (n=32,47)	13	27		
End of trial (n=34,51)	14	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Serious Adverse Events

End point title	Frequency of Serious Adverse Events
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End point description:

Frequency of serious adverse events after 50 ED, after 100 ED, and at end of trial is presented. A serious adverse event was an experience that at any dose resulted in: death; life-threatening experience; in-patient hospitalisation or prolongation of existing hospitalisation; a persistent or significant disability/incapacity; congenital anomaly/birth defect; important medical events that may not result in death, be life-threatening/require hospitalisation could be considered a serious adverse event based upon appropriate medical judgement. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events per patient years of exposure				
number (not applicable)				
50 ED (n=24,28)	0.59	0.28		
100 ED (n=32,47)	0.59	0.22		
End of trial (n=34,51)	0.58	0.15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Medical Events of Special Interest

End point title	Number of Medical Events of Special Interest
End point description:	
Number of medical events of special interest after 50 ED, after 100 ED, and at end of trial is presented. A medical event of special interest (MESI) was an event that, in the evaluation of safety, has a special focus. A MESI was an adverse event (serious or non-serious adverse event) that fulfils one or more of the MESI criteria. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.	
End point type	Secondary
End point timeframe:	
When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial	

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events				
number (not applicable)				
50 ED (n=24,28)	5	9		
100 ED (n=32,47)	6	31		
End of trial (n=34,51)	6	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Medical Events of Special Interest

End point title	Frequency of Medical Events of Special Interest
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End point description:

Frequency of medical events of special interest after 50 ED, after 100 ED, and at end of trial is presented. A medical event of special interest (MESI) was an event that, in the evaluation of safety, has a special focus. A MESI was an adverse event (serious or non-serious adverse event) that fulfils one or more of the MESI criteria. Safety analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Events per patient years of exposure				
number (not applicable)				
50 ED (n=24,28)	0.33	0.18		
100 ED (n=32,47)	0.27	0.26		
End of trial (n=34,51)	0.25	0.20		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Breakthrough Bleeding Episodes During Prophylaxis (Annualised Bleeding Rate)

End point title	Number of Breakthrough Bleeding Episodes During Prophylaxis (Annualised Bleeding Rate) ^[4]
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End point description:

Number of breakthrough bleeding episodes during prophylaxis (annualised bleeding rate) after 50 ED, after 100 ED, and at end of trial is presented. Annualised bleeding rate is the number of bleeding episodes per year. Full analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only for ABR during prophylaxis hence the pre-prophylaxis arm is not included.

End point values	Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: bleeds/subject/year				
median (full range (min-max))				
50 ED (n=28)	0.00 (0.00 to 2.60)			
100 ED (n=47)	0.25 (0.00 to 17.39)			
End of trial (n=51)	0.33 (0.00 to 17.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic Effect by 4-point Haemostatic Response Scale ("Excellent", "Good", "Moderate" and "Poor")

End point title	Haemostatic Effect by 4-point Haemostatic Response Scale ("Excellent", "Good", "Moderate" and "Poor")
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End point description:

Haemostatic effect by 4-point haemostatic response scale after 50 ED, after 100 ED, and at end of trial is presented. The haemostatic response after treatment of a bleed with nonacog beta pegol was evaluated on a 4-point scale as excellent, good, moderate or poor. Excellent: abrupt pain relief and/or clear improvement in objective signs of bleeding; Good: noticeable pain relief and/or improvement in signs of bleeding; Moderate: probable or slight beneficial effect after the first injection; Poor: no improvement or worsening of symptoms. If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or poor, the treatment was considered a failure. Full analysis set included all subjects exposed to nonacog beta pegol. n= Subjects evaluated for this endpoint at the given time point.

End point type	Secondary
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End point timeframe:

When minimum 20 PUPs have reached at least 50 ED; when minimum 40 PUPs have reached at least 100 ED; at end of trial

End point values	Pre-prophylaxis	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	51		
Units: Number of bleeds				
number (not applicable)				
50 ED (n=24,28) Excellent	23	9		
50 ED (n=24,28) Good	8	5		
50 ED (n=24,28) Moderate	2	1		
50 ED (n=24,28) Poor	0	0		
100 ED (n=32,47) Excellent	44	44		
100 ED (n=32,47) Good	17	30		
100 ED (n=32,47) Moderate	2	3		
100 ED (n=32,47) Poor	0	0		
End of trial (n=34,51) Excellent	45	86		
End of trial (n=34,51) Good	18	45		

End of trial (n=34,51) Moderate	2	4		
End of trial (n=34,51) Poor	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 434

Adverse event reporting additional description:

All presented adverse events are treatment emergent adverse events, defined as an event that occurred while the subject was on treatment in the period from first dosing with nonacog beta pegol to the end of trial/discontinuation of treatment. Safety analysis set included all subjects exposed to nonacog beta pegol.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Reporting groups

Reporting group title	Prophylaxis
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Reporting group description:

Subjects who started with pre-prophylaxis were switched to prophylaxis no later than 24 months of age or upon reaching 20EDs, whichever came first. Other subjects who started directly on prophylaxis since visit 1 received once weekly dosing of nonacog beta pegol 40 IU/kg intravenous injection in the main phase, extension phase, and until the end of treatment.

Reporting group title	Pre-prophylaxis
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Reporting group description:

Subjects received nonacog beta pegol 40 international units/kilogram (IU/kg) intravenous injection at intervals longer than a week on-demand for bleeding episodes until they were 24 months of age or until 20 exposure days (ED), whichever came first, in the main phase. Subjects switched from pre-prophylaxis treatment to prophylaxis treatment no later than 24 months of age/20 ED, whichever came first.

Serious adverse events	Prophylaxis	Pre-prophylaxis	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 51 (37.25%)	9 / 34 (26.47%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Catheterisation cardiac			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood culture positive			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 51 (1.96%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Poor venous access			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Language disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 51 (1.96%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Factor IX inhibition			
subjects affected / exposed	2 / 51 (3.92%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet dysfunction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	2 / 51 (3.92%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Autism spectrum disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			

subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media viral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prophylaxis	Pre-prophylaxis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 51 (90.20%)	22 / 34 (64.71%)	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	7 / 51 (13.73%)	0 / 34 (0.00%)	
occurrences (all)	10	0	
Fall			
subjects affected / exposed	8 / 51 (15.69%)	1 / 34 (2.94%)	
occurrences (all)	14	1	
Contusion			
subjects affected / exposed	6 / 51 (11.76%)	0 / 34 (0.00%)	
occurrences (all)	16	0	
Arthropod bite			
subjects affected / exposed	6 / 51 (11.76%)	0 / 34 (0.00%)	
occurrences (all)	7	0	
Thermal burn			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Skin laceration			
subjects affected / exposed	4 / 51 (7.84%)	1 / 34 (2.94%)	
occurrences (all)	9	1	
Lip injury			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	11	0	
Speech disorder developmental			

subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5	0 / 34 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	27 / 51 (52.94%) 74	11 / 34 (32.35%) 23	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 5	1 / 34 (2.94%) 1	
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	0 / 34 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6 11 / 51 (21.57%) 13 5 / 51 (9.80%) 7 4 / 51 (7.84%) 8 11 / 51 (21.57%) 15 4 / 51 (7.84%) 7	0 / 34 (0.00%) 0 3 / 34 (8.82%) 3 0 / 34 (0.00%) 0 0 / 34 (0.00%) 0 2 / 34 (5.88%) 2 1 / 34 (2.94%) 3	
Respiratory, thoracic and mediastinal disorders Epistaxis			

subjects affected / exposed	3 / 51 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Cough			
subjects affected / exposed	17 / 51 (33.33%)	4 / 34 (11.76%)	
occurrences (all)	34	5	
Rhinorrhoea			
subjects affected / exposed	9 / 51 (17.65%)	3 / 34 (8.82%)	
occurrences (all)	21	5	
Rhinitis allergic			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Oropharyngeal pain			
subjects affected / exposed	4 / 51 (7.84%)	0 / 34 (0.00%)	
occurrences (all)	8	0	
Nasal congestion			
subjects affected / exposed	4 / 51 (7.84%)	1 / 34 (2.94%)	
occurrences (all)	16	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Eczema			
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
Rash			
subjects affected / exposed	6 / 51 (11.76%)	3 / 34 (8.82%)	
occurrences (all)	14	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 34 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 51 (9.80%)	0 / 34 (0.00%)	
occurrences (all)	6	0	
Hand-foot-and-mouth disease			

subjects affected / exposed	4 / 51 (7.84%)	0 / 34 (0.00%)
occurrences (all)	4	0
Gastroenteritis		
subjects affected / exposed	4 / 51 (7.84%)	0 / 34 (0.00%)
occurrences (all)	4	0
Ear infection		
subjects affected / exposed	9 / 51 (17.65%)	3 / 34 (8.82%)
occurrences (all)	13	4
Conjunctivitis		
subjects affected / exposed	4 / 51 (7.84%)	1 / 34 (2.94%)
occurrences (all)	6	1
COVID-19		
subjects affected / exposed	6 / 51 (11.76%)	0 / 34 (0.00%)
occurrences (all)	7	0
Bronchitis		
subjects affected / exposed	6 / 51 (11.76%)	1 / 34 (2.94%)
occurrences (all)	8	1
Viral infection		
subjects affected / exposed	5 / 51 (9.80%)	3 / 34 (8.82%)
occurrences (all)	10	3
Tonsillitis		
subjects affected / exposed	5 / 51 (9.80%)	1 / 34 (2.94%)
occurrences (all)	8	1
Sinusitis		
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)
occurrences (all)	5	0
Rhinitis		
subjects affected / exposed	3 / 51 (5.88%)	0 / 34 (0.00%)
occurrences (all)	4	0
Pharyngitis		
subjects affected / exposed	4 / 51 (7.84%)	1 / 34 (2.94%)
occurrences (all)	4	1
Otitis media acute		
subjects affected / exposed	5 / 51 (9.80%)	2 / 34 (5.88%)
occurrences (all)	5	4
Otitis media		

subjects affected / exposed	6 / 51 (11.76%)	2 / 34 (5.88%)	
occurrences (all)	12	2	
Nasopharyngitis			
subjects affected / exposed	23 / 51 (45.10%)	5 / 34 (14.71%)	
occurrences (all)	68	12	
Upper respiratory tract infection			
subjects affected / exposed	19 / 51 (37.25%)	5 / 34 (14.71%)	
occurrences (all)	33	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2015	This amendment allowed major surgery, specified requirements for major surgery and the data items to be recorded, ensured that genotyping of the haemophilia B mutation was collected, and minor clarifications and corrections to protocol version 1.0.
15 February 2017	This amendment specified the change in the colour of the reconstituted solution from "clear and colourless to slightly yellow solution" to "clear and colourless solution free from clearly visible particles".
30 January 2018	This amendment included following parameters: neurological examination, biochemistry analysis, polyethylene glycol analysis and height to certain visits. Subject participation in the trial was also clarified. It was also specified that all central nervous system related adverse events (AEs) were to be categorised as medical event of special interest (MESI).
11 October 2018	This amendment included neurocognitive assessments and specified that all renal AEs were to be categorised as MESI.
17 December 2019	This amendment extended the recruitment period to increase the number of subjects on trial product to increase the number of baseline neurocognitive assessments collected in the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported