Clinical trial results:
Safety, Efficacy and Pharmacokinetics of NNC-0156-0000-0009 (N9-GP) in Previously Treated Children with Haemophilia B

Summary

EudraCT number	2011-000826-31
Trial protocol	DE GB IT
Global end of trial date	17 November 2023

Results information

Result version number	v1 (current)
This version publication date	01 June 2024
First version publication date	01 June 2024

Trial information

Trial identification

Sponsor protocol code	NN7999-3774

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01467427
WHO universal trial number (UTN)	U1111-1119-5013
Other trial identifiers	Japanese trial registration: JapicCTI-121877

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)	EMEA-000731-PIP09-03
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	03 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate immunogenicity of glycopegylated recombinant coagulation factor IX (NNC-0156-0000-0009; hereafter referred to as nonacog beta pegol [N9-GP])

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki 2013 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents 1996 and 21 US Code of Federal Regulations (CFR) 312.120.50 and 56.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 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	Canada: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	25
EEA total number of subjects	2

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	3

months)	
Children (2-11 years)	20
Adolescents (12-17 years)	2
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 19 sites in 8 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): Canada (1/ 1); Germany (1/ 1); Italy (1/ 1); Japan (3/ 3); Malaysia (1/ 1); Taiwan (1/ 1); United Kingdom (3/ 3); United States (8/ 6).

Pre-assignment

Screening details:

The trial consisted of a main phase/core study (Visit 1 – Visit 11) and an extension phase (Visit 12 – end of trial).

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?	Yes
Arm title	Younger children (0-6 years)

Arm description:

Subjects (0-6 years) received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

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

Dosage and administration details:

Nonacog beta pegol 40 IU/kg intravenous (i.v.) injection was administered once weekly and as on-demand treatment for bleeds for the main and extension phases.

Arm title	Older children (7-12 years)

Arm description:

Subjects (7-12 years) received nonacog beta pegol 40 IU/kg i.v. injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

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

Dosage and administration details:

Nonacog beta pegol 40 IU/kg i.v. injection was administered once weekly and as on-demand treatment for bleeds for the main and extension phases.

Number of subjects in period 1	Younger children (0-6 years)	Older children (7-12 years)
Started	12	13
Full analysis set	12	13
Safety analysis set	12	13
Completed main phase	11	13
Entered extension phase	11	11
Completed	6	4
Not completed	6	9
Consent withdrawn by subject	3	1
Subject moved out of province	-	1
Subject's caregiver decision	1	-
Discontinuation of PI at site	1	-
Study closed due to staff	1	-
Withdrawal criteria	-	4
Non-compliance	-	1
Lost to follow-up	-	1
Consent withdrawn by parent	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Younger children (0-6 years)
Reporting group description:	
Subjects (0-6 years) received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.	
Reporting group title	Older children (7-12 years)
Reporting group description:	
Subjects (7-12 years) received nonacog beta pegol 40 IU/kg i.v. injection once weekly and as on-demand treatment for bleeds for the main and extension phases.	

Reporting group values	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of subjects	12	13	25
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	3	0	3
Children (2-11 years)	9	11	20
Adolescents (12-17 years)	0	2	2
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	3.1	9.6	
standard deviation	± 1.7	± 1.6	-
Gender Categorical Units: Subjects			
Female	0	0	0
Male	12	13	25

End points

End points reporting groups

Reporting group title	Younger children (0-6 years)
Reporting group description:	
Subjects (0-6 years) received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.	
Reporting group title	Older children (7-12 years)
Reporting group description:	
Subjects (7-12 years) received nonacog beta pegol 40 IU/kg i.v. injection once weekly and as on-demand treatment for bleeds for the main and extension phases.	

Primary: Incidence of Inhibitory Antibodies Against Coagulation Factor IX (FIX) Defined as Titre Greater Than or Equal To (≥) 0.6 Bethesda Unit (BU)

End point title	Incidence of Inhibitory Antibodies Against Coagulation Factor IX (FIX) Defined as Titre Greater Than or Equal To (≥) 0.6 Bethesda Unit (BU)[1]
End point description:	
Number of subjects who developed inhibitory antibodies against factor IX are reported. Inhibitors were analysed with either the Nijmegen modified factor IX Bethesda assay or a heat/cold Nijmegen modified factor IX Bethesda assay. Safety analysis set included all subjects exposed to nonacog beta pegol.	
End point type	Primary
End point timeframe:	
Week 52	

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	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Episodes During Prophylaxis

End point title	Number of Bleeding Episodes During Prophylaxis
End point description:	
Number of bleeding episodes per subject during routine prophylaxis was assessed using the individual annualised bleeding rates (bleeding episodes per subject per year). Full analysis set (FAS) included all subjects with efficacy data after exposure to nonacog beta pegol.	
End point type	Secondary
End point timeframe:	
Week 52	

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: bleeds/subject/year				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 1.78)	2.00 (0.68 to 2.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic Effect of N9-GP in Treatment of Bleeding Episodes by 4-point Categorical Scale for Haemostatic Response (Excellent, Good, Moderate and Poor)

End point title	Haemostatic Effect of N9-GP in Treatment of Bleeding Episodes by 4-point Categorical Scale for Haemostatic Response (Excellent, Good, Moderate and Poor)

End point description:

Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes was measured and listed according to the four-point scale for haemostatic response as: Excellent – abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single infusion; Good – noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection; Moderate – probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one infusion within 8 hours; Poor – no improvement, or worsening of symptoms within 8 hours after two injections. FAS included all subjects with efficacy data after exposure to nonacog beta pegol.

End point type	Secondary

End point timeframe:

Week 52

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Bleeding episodes				
number (not applicable)				
Excellent	7	15		
Good	3	14		
Moderate	0	2		
Poor	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery at 30 Minutes (IR30min)

End point title	Incremental Recovery at 30 Minutes (IR30min)

End point description:

Incremental recovery at 30 min was calculated by dividing the factor IX activity units per millilitre (U/mL) measured in plasma 30 min after dosing by the dose injected at time 0 expressed as units per kilogram (U/kg) body weight. FAS included all subjects with efficacy data after exposure to nonacog beta pegol. Number of Subjects Analyzed = subjects who were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Week 0

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	13		
Units: (U/mL)/(U/kg)				
geometric mean (geometric coefficient of variation)	0.015 (± 7.31)	0.016 (± 16.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Level Single-dose

End point title	Trough Level Single-dose

End point description:

The lowest activity of factor IX recorded at week 0, 168 hours post-dose (immediately before next dose was given) is reported. FAS included all subjects with efficacy data after exposure to nonacog beta pegol. Number of Subjects Analyzed = subjects who were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Week 0

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: Units per millitre (U/mL)				
geometric mean (geometric coefficient of variation)	0.084 (± 16.28)	0.109 (± 18.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t1/2)

End point title	Terminal Half-life (t1/2)

End point description:

Terminal half-life was calculated as natural log [ln](2)/λz, where λz is the terminal elimination rate. The terminal elimination rate was estimated using linear regression on the terminal part of the log(activity) versus time profile. FAS included all subjects with efficacy data after exposure to nonacog beta pegol.

End point type	Secondary

End point timeframe:

Week 0

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: hours				
geometric mean (geometric coefficient of variation)	69.576 (± 15.79)	76.323 (± 25.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Level Steady State

End point title	Trough Level Steady State

End point description:

The lowest activity recorded immediately before next dose was given after week 1 i.e. from week 4 to week 52. The analysis is based on a mixed model on the log-transformed plasma concentrations with subject as a random effect. The mean trough level is presented back-transformed to the natural scale. FAS included all subjects with efficacy data after exposure to nonacog beta pegol.

End point type	Secondary

End point timeframe:

Week 4 to Week 52

End point values	Younger children (0-6 years)	Older children (7-12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Units per millitre (U/mL)				
arithmetic mean (confidence interval 95%)	0.154 (0.127 to 0.186)	0.190 (0.159 to 0.228)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to year 12

Adverse event reporting additional description:

All presented adverse events are treatment emergent adverse events, defined as as adverse event occurring after dosing with trial product. Safety analysis set included all subjects exposed to nonacog beta pegol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Younger children (0 - 6 years)

Reporting group description:

Subjects received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

Reporting group title	Older children (7 - 12 years)

Reporting group description:

Subjects received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

Reporting group title	Adolescents (13 - 17 years)

Reporting group description:

Subjects received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

Reporting group title	Adults (18 - 70 years)

Reporting group description:

Subjects received nonacog beta pegol 40 international units per kilogram (IU/kg) intravenous (i.v.) injection once weekly and as on-demand treatment for bleeds for the main and extension phases.

Serious adverse events	Younger children (0 - 6 years)	Older children (7 - 12 years)	Adolescents (13 - 17 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	5 / 23 (21.74%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Vascular disorders			
Arteriovenous fistula			

subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Tourette's disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter site infection			

subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 14 (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
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Adults (18 - 70 years)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cryptorchism			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tourette's disorder				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Migraine				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Food poisoning				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Haemoptysis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wheezing				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Catheter site infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Younger children (0 - 6 years)	Older children (7 - 12 years)	Adolescents (13 - 17 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	20 / 23 (86.96%)	12 / 14 (85.71%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site irritation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	7	0
Pyrexia			
subjects affected / exposed	7 / 12 (58.33%)	6 / 23 (26.09%)	2 / 14 (14.29%)
occurrences (all)	18	14	2
Immune system disorders			

Allergy to arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	3 / 12 (25.00%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	3	2	0
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Penile discharge			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nipple disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 12 (83.33%)	6 / 23 (26.09%)	1 / 14 (7.14%)
occurrences (all)	23	8	1
Catarrh			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	4	1	0
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	6	2	0
Oropharyngeal pain			
subjects affected / exposed	3 / 12 (25.00%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	5	5	0
Rhinorrhoea			

subjects affected / exposed	2 / 12 (16.67%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	11	1	1
Rhinitis allergic			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	6	1	1
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Sleep terror			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Varicella virus test positive			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Arthropod bite			

subjects affected / exposed	2 / 12 (16.67%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Accident			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	3 / 12 (25.00%)	7 / 23 (30.43%)	1 / 14 (7.14%)
occurrences (all)	12	16	1
Clavicle fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	3 / 12 (25.00%)	4 / 23 (17.39%)	0 / 14 (0.00%)
occurrences (all)	4	5	0
Ear injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	2 / 12 (16.67%)	6 / 23 (26.09%)	1 / 14 (7.14%)
occurrences (all)	9	9	1
Hand fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Immunisation reaction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	0	1	5
Injury			
subjects affected / exposed	1 / 12 (8.33%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	1	7	0
Joint dislocation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Joint injury			
subjects affected / exposed	1 / 12 (8.33%)	3 / 23 (13.04%)	2 / 14 (14.29%)
occurrences (all)	1	16	2
Ligament sprain			

subjects affected / exposed	2 / 12 (16.67%)	5 / 23 (21.74%)	3 / 14 (21.43%)
occurrences (all)	2	9	8
Limb injury			
subjects affected / exposed	2 / 12 (16.67%)	4 / 23 (17.39%)	2 / 14 (14.29%)
occurrences (all)	2	11	3
Lip injury			
subjects affected / exposed	2 / 12 (16.67%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nasal injury			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Muscle strain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Post procedural swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Neck injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Product administration error			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Post-traumatic pain			
subjects affected / exposed	2 / 12 (16.67%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	3	7	0
Skin laceration			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	1 / 14 (7.14%)
occurrences (all)	1	3	1
Skin injury			

subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	4 / 12 (33.33%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	5	7	0
Road traffic accident			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Traumatic haematoma			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Thermal burn			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Traumatic haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	4	2	0
Wound			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	4 / 23 (17.39%)	3 / 14 (21.43%)
occurrences (all)	0	12	4
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Hypoacusis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Myopia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	3	1	0
Dental caries			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Enteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	5	2	0
Haematochezia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lip swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)	4 / 23 (17.39%)	0 / 14 (0.00%)
occurrences (all)	8	7	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Haemorrhage subcutaneous			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Nail disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Rash			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	4
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	5 / 23 (21.74%)	3 / 14 (21.43%)
occurrences (all)	0	16	4
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Growing pains			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Joint swelling			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	6 / 23 (26.09%)	2 / 14 (14.29%)
occurrences (all)	3	13	2
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Synovitis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
COVID-19			
subjects affected / exposed	0 / 12 (0.00%)	3 / 23 (13.04%)	2 / 14 (14.29%)
occurrences (all)	0	4	2
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	1 / 14 (7.14%)
occurrences (all)	3	2	1
Bronchiolitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Croup infectious			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	3 / 12 (25.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	4	2	0
Diarrhoea infectious			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	2 / 12 (16.67%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	2 / 23 (8.70%)	3 / 14 (21.43%)
occurrences (all)	1	5	5
Keratouveitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Localised infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Nasopharyngitis			
subjects affected / exposed	5 / 12 (41.67%)	4 / 23 (17.39%)	2 / 14 (14.29%)
occurrences (all)	14	17	2
Myringitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	2 / 12 (16.67%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	2	3	0
Pharyngitis streptococcal			
subjects affected / exposed	3 / 12 (25.00%)	3 / 23 (13.04%)	0 / 14 (0.00%)
occurrences (all)	6	6	0
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Otitis media acute			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	3 / 12 (25.00%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	5	0	0
Pulpitis dental			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Streptococcal infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0

Tooth abscess			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 23 (8.70%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Varicella zoster virus infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	1 / 12 (8.33%)	1 / 23 (4.35%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	3 / 23 (13.04%)	1 / 14 (7.14%)
occurrences (all)	6	4	4

Non-serious adverse events	Adults (18 - 70 years)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site irritation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Penile discharge			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nipple disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Catarrh			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Wheezing subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Psychiatric disorders Attention deficit hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Sleep terror subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Product issues Device occlusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Cardiac murmur subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Varicella virus test positive subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Injury, poisoning and procedural complications			

Abdominal injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Arthropod bite				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Accident				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Contusion				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Clavicle fracture				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Fall				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ear injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Head injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Hand fracture				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Immunisation reaction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Joint dislocation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Joint injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ligament sprain				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Limb injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lip injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nasal injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Muscle strain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Post procedural swelling				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Neck injury				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Product administration error				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Procedural pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Post-traumatic pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Skin laceration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Skin injury subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Skin abrasion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Road traffic accident subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Radius fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Traumatic haematoma subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Thermal burn subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Traumatic haemorrhage subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Wound subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Migraine			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myopia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Enteritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Diarrhoea			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Lip swelling			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Nail disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Rash subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Urticaria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Renal impairment subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Groin pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Growing pains subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Joint swelling subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Myalgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Neck pain			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Synovitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bronchiolitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Croup infectious			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Diarrhoea infectious			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Keratouveitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Localised infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Myringitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Otitis media acute				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Pulpitis dental				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Streptococcal infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Varicella zoster virus infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2012	Protocol was updated based on changes in the description of the visual appearance of the investigational medicinal product and information on stop time of bleeds.
22 September 2013	Protocol was updated based on change of the planned subject tailored nonacog beta pegol dose in the extension phase to a fixed dose of 40 IU/kg once weekly and some minor changes.
26 September 2014	Protocol was updated based on the following: major surgery could be performed as part of the trial; all subjects were switched from the current nonacog beta pegol to nonacog beta pegol intended for commercial use; optional blood samples for potential future assessments were drawn to address safety or efficacy, anti-drug antibody assessments and to improve the understanding of the mechanisms of action.
26 February 2015	Protocol was updated based on: total blood volume drawn at each visit in the extension phase was corrected; bio specimen for storage for genotype was added to flowchart; clarification on the dispensing visits, patient reported outcomes (PRO) questionnaires and other changes; timelines changed.
23 January 2017	Protocol was updated based on update in the colour of the nonacog beta pegol drug product; elaboration to the allergic reaction testing to align with the already described procedure in the flowchart.
27 February 2018	Protocol was updated based on: measurement of polyethylene glycol were added at every prospective visit; last subject last visit of the trial was extended to 2023 to allow the subjects to continue up to visit 32 and the youngest child to reach up to 12 years of age; new (and additional) age-appropriate PRO introduced at visit 17 and repeated at end of trial; monitoring visit frequency was prolonged to every 28 weeks and a phone call or other contact between parents and site staff was allowed; definition of incremental recovery was clarified and other minor changes to text.
29 September 2018	Protocol was updated based on: addition of neurocognitive assessments in the protocol; renal adverse events were categorised as medical events of special interest; PRO were added at the relevant visit where neurocognitive assessments were performed for the first time in each subject and at end of trial visit; chromogenic assay was no longer used by the central laboratory.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported