Clinical trial results:
A multicenter Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe haemophilia A under prophylaxis therapy

Summary

EudraCT number	2010-021781-29
Trial protocol	HU LT SE DK IE LV BG IT PL AT ES GB NO
Global end of trial date	27 October 2020

Results information

Result version number	v3 (current)
This version publication date	02 December 2021
First version publication date	22 March 2020
Version creation reason	• Correction of full data set Correction needed for full data set

Trial information

Trial identification

Sponsor protocol code	BAY81-8973/13400

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01311648
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001064-PIP01-10
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	27 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and efficacy of the treatment with BAY81-8973 for prophylaxis and treatment of breakthrough bleeds in children with severe hemophilia A

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects/legal representatives. Participating subjects/legal representatives signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The assent of a minor was also requested where such a person was able to express his own will. His refusal or the withdrawal of his consent was not to be disregarded. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Canada: 6

Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Russian Federation: 5
Worldwide total number of subjects	94
EEA total number of subjects	66

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	37
Children (2-11 years)	53
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 study was conducted at multiple centers in 18 countries and consisted of: Part A main study - between 09-JUN-2011 (FPFV) and 02-JAN-2013 (LPLV); Part B main study - between 19-SEP-2012 (FPFV) and 09-SEP-2019 (LPLV); extension study - between 21-DEC-2011 (FPFV) and 27-OCT-2020 (LPLV).

Pre-assignment

Screening details:

Overall, 58 subjects were screened in Part A, of which 7 subjects were screening failures and 51 subjects received the study drug; 52 subjects were screened in Part B, of which 9 subjects were screening failures and 43 subjects received the study drug. 46 subjects from Part A and 36 from Part B entered the optional extension study.

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	Main study - Part A: PTPs 0-<6 years

Arm description:

Previously treated patients (PTPs) aged below 6 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY81-8973
Other name	Kovaltry
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25-50 IU/kg at least 2x/week for 6 months and at least 50 EDs, intravenous (IV) infusion. Exposure day (ED): An ED is a unit of time (1 day) in which replacement treatment of Hemophilia is given to a patient.

Arm title	Main study - Part A: PTPs 6-12 years

Arm description:

Previously treated patients (PTPs) aged 6 to 12 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY81-8973
Other name	Kovaltry
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25-50 IU/kg at least 2x/week for 6 months and at least 50 EDs, IV infusion

Arm title	Main study - Part B: PUPs/MTPs 0-<6 years

Arm description:

Previously untreated patients (PUPs) or minimally treated patients (MTPs, patients who had no more than 3 exposure days (EDs) with any FVIII product) received BAY81-8973 15-50 IU/kg at least 1x/week for at least 50 EDs or until inhibitor development in main study - Part B.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY81-8973
Other name	Kovaltry
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-50 IU/kg at least 1x/week for at least 50 EDs or until inhibitor development, IV infusion

Arm title	Extension study – former Part A subjects

Arm description:

Subjects having reached at least 50 exposure days (EDs) in main study - Part A were offered participation in an open label extension study (optional). Subjects who transitioned from main study - Part A to the extension study received BAY81-8973, 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part A and extension study).

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY81-8973
Other name	Kovaltry
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part A and extension study), IV infusion

Arm title	Extension study – former Part B subjects

Arm description:

Subjects having reached at least 50 exposure days (EDs) in main study - Part B were offered participation in an open label extension study and received BAY81-8973 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part B and extension study); subjects who developed an inhibitor in main study - Part B were offered participation in open label extension study and received Immune Tolerance Induction (ITI) treatment with BAY81-8973 until successful eradication of the inhibitor, or until failure, for approximately 18 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY81-8973
Other name	Kovaltry
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For subjects having reached at least 50 EDs in main study - Part B: 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part B and extension study), IV infusion. For subjects who developed an inhibitor in main study - Part B: up to 200 IU/kg per day or 100 IU/kg twice a day at the discretion of the investigator and coordinating investigator until successful eradication of the inhibitor, or until failure, for up to 18 months (treatment beyond 18 months required an agreement with the sponsor and coordinating investigator), IV infusion.

Number of subjects in period 1	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years
Started	25	26	43
Completed	25	26	22
Not completed	0	0	21
Consent withdrawn by subject	-	-	2

Physician decision	-	-	-
Inhibitor management	-	-	17
Failure of ITI therapy	-	-	-
Long travel	-	-	-
Adverse event	-	-	1
Family's decision	-	-	-
ITI therapy with marketed product	-	-	-
Incorrect visit planning	-	-	-
Protocol deviation	-	-	1
Diagnosed with von Willebrand Disease	-	-	-

Number of subjects in period 1	Extension study – former Part A subjects	Extension study – former Part B subjects
Started	46	36
Completed	45	25
Not completed	1	11
Consent withdrawn by subject	-	1
Physician decision	-	1
Inhibitor management	-	2
Failure of ITI therapy	-	3
Long travel	-	1
Adverse event	-	-
Family's decision	-	1
ITI therapy with marketed product	-	1
Incorrect visit planning	-	1
Protocol deviation	-	-
Diagnosed with von Willebrand Disease	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Main study - Part A: PTPs 0-<6 years
Reporting group description:	
Previously treated patients (PTPs) aged below 6 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.	
Reporting group title	Main study - Part A: PTPs 6-12 years
Reporting group description:	
Previously treated patients (PTPs) aged 6 to 12 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.	
Reporting group title	Main study - Part B: PUPs/MTPs 0-<6 years
Reporting group description:	
Previously untreated patients (PUPs) or minimally treated patients (MTPs, patients who had no more than 3 exposure days (EDs) with any FVIII product) received BAY81-8973 15-50 IU/kg at least 1x/week for at least 50 EDs or until inhibitor development in main study - Part B.	
Reporting group title	Extension study – former Part A subjects
Reporting group description:	
Subjects having reached at least 50 exposure days (EDs) in main study - Part A were offered participation in an open label extension study (optional). Subjects who transitioned from main study - Part A to the extension study received BAY81-8973, 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part A and extension study).	
Reporting group title	Extension study – former Part B subjects
Reporting group description:	
Subjects having reached at least 50 exposure days (EDs) in main study - Part B were offered participation in an open label extension study and received BAY81-8973 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part B and extension study); subjects who developed an inhibitor in main study - Part B were offered participation in open label extension study and received Immune Tolerance Induction (ITI) treatment with BAY81-8973 until successful eradication of the inhibitor, or until failure, for approximately 18 months.	

Reporting group values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years
Number of subjects	25	26	43
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	3.8	8.8	1.1
standard deviation	± 1.3	± 1.8	± 0.8
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	25	26	43
Race			
Units: Subjects			
White	24	24	37
Black	1	2	1
American Indian or Alaska native	0	0	1
White, American Indian or Alaska native	0	0	1

Not reported	0	0	3
Ethnicity Units: Subjects			
Not Hispanic or Latino	23	25	34
Hispanic or Latino	1	0	9
Not reported	1	1	0

Reporting group values	Extension study – former Part A subjects	Extension study – former Part B subjects	Total
Number of subjects	46	36	94
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.3	1.1	
standard deviation	± 3.0	± 0.5	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	46	36	94
Race Units: Subjects			
White	43	32	85
Black	3	0	4
American Indian or Alaska native	0	1	1
White, American Indian or Alaska native	0	1	1
Not reported	0	2	3
Ethnicity Units: Subjects			
Not Hispanic or Latino	43	30	82
Hispanic or Latino	1	6	10
Not reported	2	0	2

End points

End points reporting groups

Reporting group title	Main study - Part A: PTPs 0-<6 years
Reporting group description:	
Previously treated patients (PTPs) aged below 6 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.	
Reporting group title	Main study - Part A: PTPs 6-12 years
Reporting group description:	
Previously treated patients (PTPs) aged 6 to 12 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.	
Reporting group title	Main study - Part B: PUPs/MTPs 0-<6 years
Reporting group description:	
Previously untreated patients (PUPs) or minimally treated patients (MTPs, patients who had no more than 3 exposure days (EDs) with any FVIII product) received BAY81-8973 15-50 IU/kg at least 1x/week for at least 50 EDs or until inhibitor development in main study - Part B.	
Reporting group title	Extension study – former Part A subjects
Reporting group description:	
Subjects having reached at least 50 exposure days (EDs) in main study - Part A were offered participation in an open label extension study (optional). Subjects who transitioned from main study - Part A to the extension study received BAY81-8973, 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part A and extension study).	
Reporting group title	Extension study – former Part B subjects
Reporting group description:	
Subjects having reached at least 50 exposure days (EDs) in main study - Part B were offered participation in an open label extension study and received BAY81-8973 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part B and extension study); subjects who developed an inhibitor in main study - Part B were offered participation in open label extension study and received Immune Tolerance Induction (ITI) treatment with BAY81-8973 until successful eradication of the inhibitor, or until failure, for approximately 18 months.	
Subject analysis set title	Safety analysis set (SAF) - A
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who entered main study - Part A and received at least one infusion of study medication.	
Subject analysis set title	Safety analysis set (SAF) - B
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who entered main study - Part B and received at least one infusion of study medication	
Subject analysis set title	Intent-to-treat (ITT) analysis set - A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects of the SAF-A who had infusion/bleeding data from the electronic patient diary (EPD)	
Subject analysis set title	Intent-to-treat (ITT) analysis set - B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects of the SAF-B who had infusion/bleeding data from the electronic patient diary (EPD)	
Subject analysis set title	PK analysis set (PKS) - A
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who entered main study - Part A and received at least one infusion of study medication with evaluable pharmacokinetic (PK) data	
Subject analysis set title	ITT - Extension - former Part A subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who entered the extension study from main study - Part A

Subject analysis set title	ITT - Extension - former Part B subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who entered the extension study from main study - Part B

Primary: Annualized number of total bleeds within 48 h

End point title	Annualized number of total bleeds within 48 h[1][2]

End point description:

Annualized number (mean +/- standard deviation) of total bleeds that occurred within 48 hours after all prophylaxis infusions (Part A: 6 months and at least 50 exposure days [EDs]; Part B: at least 50 EDs or until inhibitor development) was summarized and reported. Total bleeds: sum of spontaneous bleeds, trauma bleeds (only treated bleeds were classified as spontaneous or trauma), untreated bleeds and 'other' bleeds ('other' bleeds were infusions with reason given as 'other').

End point type	Primary

End point timeframe:

Within 48 hours post infusion

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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.
[2] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[3]	26[4]	43[5]	
Units: bleed(s)				
arithmetic mean (standard deviation)	2.23 (± 2.77)	1.86 (± 3.08)	1.9 (± 3.3)	

Notes:

[3] - ITT-A

[4] - ITT-A

[5] - ITT-B

Statistical analyses

No statistical analyses for this end point

Primary: Annualized number of total bleeds within 48 h

End point title	Annualized number of total bleeds within 48 h[6][7]

End point description:

Annualized number (median [inter-quartile range (Q1-Q3)]) of total bleeds that occurred within 48 hours after all prophylaxis infusions (Part A: 6 months and at least 50 exposure days [EDs]; Part B: at least 50 EDs or until inhibitor development) was summarized and reported. Total bleeds: sum of spontaneous bleeds, trauma bleeds (only treated bleeds were classified as spontaneous or trauma), untreated bleeds and 'other' bleeds ('other' bleeds were infusions with reason given as 'other').

End point type	Primary

End point timeframe:

Within 48 hours post infusion

Notes:

[6] - 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: Due to the nature of this trial and due to the limited sample size, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.
[7] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[8]	26[9]	43[10]	
Units: bleed(s)				
median (inter-quartile range (Q1-Q3))	1.88 (0.00 to 3.97)	0.00 (0.00 to 1.96)	0.0 (0.0 to 2.2)	

Notes:

[8] - ITT-A

[9] - ITT-A

[10] - ITT-B

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized number of total bleeds during prophylaxis treatment

End point title	Annualized number of total bleeds during prophylaxis treatment[11]

End point description:

Annualized number (mean +/- standard deviation) of total bleeds that occurred during prophylaxis treatment was summarized and reported. Total bleeds: sum of spontaneous bleeds, trauma bleeds (only treated bleeds were classified as spontaneous or trauma), untreated bleeds and 'other' bleeds ('other' bleeds were infusions with reason given as 'other').

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[11] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[12]	26[13]	43[14]	
Units: bleed(s)				
arithmetic mean (standard deviation)	4.16 (± 5.02)	3.37 (± 5.01)	7.1 (± 8.6)	

Notes:

[12] - ITT-A

[13] - ITT-A

[14] - ITT-B

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized number of total bleeds during prophylaxis treatment

End point title	Annualized number of total bleeds during prophylaxis treatment[15]

End point description:

Annualized number (median [inter-quartile range (Q1-Q3)]) of total bleeds that occurred during prophylaxis treatment was summarized and reported. Total bleeds: sum of spontaneous bleeds, trauma bleeds (only treated bleeds were classified as spontaneous or trauma), untreated bleeds and 'other' bleeds ('other' bleeds were infusions with reason given as 'other').

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[15] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[16]	26[17]	43[18]	
Units: bleed(s)				
median (inter-quartile range (Q1-Q3))	2.03 (0.00 to 6.02)	0.93 (0.00 to 5.77)	4.7 (2.1 to 8.9)	

Notes:

[16] - ITT-A

[17] - ITT-A

[18] - ITT-B

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic control during major and minor surgeries

End point title	Hemostatic control during major and minor surgeries[19]

End point description:

For patients who underwent major or minor surgeries during the study, hemostasis during the surgeries was assessed as excellent, good, moderate or poor. Number of surgeries per assessment was summarized and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[19] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[20]	1[21]	6[22]	
Units: surgery(s)				
Minor surgery - Excellent		0	3	
Minor surgery - Good		0	1	
Minor surgery - Moderate		0	0	
Minor surgery - Poor		0	0	
Minor surgery - Not available		0	1	
Major surgery - Excellent		0	0	
Major surgery - Good		1	1	
Major surgery - Moderate		0	0	
Major surgery - Poor		0	0	
Major surgery - Not available		0	0	

Notes:

[20] - Subjects in SAF-A who underwent major or minor surgeries during the study

[21] - Subjects in SAF-A who underwent major or minor surgeries during the study

[22] - Subjects in SAF-B who underwent major or minor surgeries during the study

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with inhibitor development in main study

End point title	Number of subjects with inhibitor development in main

End point description:

Number of subjects who developed a positive FVIII inhibitor level (≥0.6 Bethesda unit [BU/mL]) during the study was summarized and classified as subjects developing low titer inhibitor (i.e. ≤ 5.0 BU/mL) and subjects developing high titer inhibitor (i.e. > 5.0 BU/mL).

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[23] - 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: The results of extension study arms are reported in a separate endpoint.

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[24]	26[25]	42[26]	
Units: subject(s)				
Low titer inhibitor	0	0	6	
High titer inhibitor	0	0	17	

Notes:

[24] - SAF-A

[25] - SAF-A

[26] - Subjects in SAF-B with inhibitor measurements done

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with inhibitor development in extension study

End point title	Number of subjects with inhibitor development in extension study[27]

End point description:

Number of subjects who had not developed an inhibitor during the main study but developed an inhibitor (confirmed positive FVIII inhibitor titer [≥ 0.6 BU/mL]) during the extension study was summarized and classified as subjects developing low titer inhibitor (i.e. ≥ 0.6 to ≤ 5.0 BU/mL) and subjects developing high titer inhibitor (i.e. > 5.0 BU/mL).

End point type	Secondary

End point timeframe:

From start of extension study to at least 100 cumulative exposure days (EDs) (median 421 EDs; median 3.8 years)

Notes:

[27] - 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: The results of main study arms are reported in a separate endpoint.

End point values	Extension study – former Part A subjects	Extension study – former Part B subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[28]	16[29]		
Units: subject(s)				
Low titer inhibitor (incl. false-positive)	1	0		
High titer inhibitor	0	0		

Notes:

[28] - ITT-Extension-former Part A subjects; the subject had a false positive inhibitor test

[29] - ITT-Extension-former Part B subjects who had not developed inhibitors during the main study - Part B

Statistical analyses

No statistical analyses for this end point

Secondary: Factor VIII recovery values

End point title	Factor VIII recovery values[30]

End point description:

Incremental recovery of Factor VIII (FVIII) at 20-30 min after end of infusions was determined and mean recovery values were reported. "99999" denotes that value was not calculated because no subject fell into the category.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[30] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[31]	26[32]	32[33]	
Units: International unit (IU)/dL per IU/kg				
arithmetic mean (standard deviation)				
Subjects without inhibitor	1.63 (± 0.31)	1.72 (± 0.46)	1.76 (± 0.55)	
Subjects with low titer inhibitor	99999 (± 99999)	99999 (± 99999)	0.86 (± 0.56)	
Subjects with high titer inhibitor	99999 (± 99999)	99999 (± 99999)	0.38 (± 0.42)	

Notes:

[31] - Subjects in ITT-A with valid FVIII recovery values

[32] - Subjects in ITT-A with valid FVIII recovery values

[33] - Subjects in ITT-B with valid FVIII recovery values

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of Factor VIII in all infusions

End point title	Consumption of Factor VIII in all infusions[34]

End point description:

Factor VIII (FVIII) usage/consumption was summarized for all infusions. Consumption per subject's body weight per year was calculated and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[34] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[35]	26[36]	43[37]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	5499.1 (± 1996.2)	4679.1 (± 1688.7)	2195.8 (± 1903.6)	

Notes:

[35] - ITT-A

[36] - ITT-A

[37] - ITT-B

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of FVIII in infusions for prophylaxis

End point title	Consumption of FVIII in infusions for prophylaxis[38]

End point description:

Factor VIII (FVIII) usage/consumption was summarized for prophylaxis infusions. Consumption per subject's body weight per year was calculated and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[38] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[39]	26[40]	42[41]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	5224.8 (± 1760.2)	4492.7 (± 1667.6)	1486.6 (± 963.3)	

Notes:

[39] - Subjects in ITT-A with at least one dose of prophylaxis treatment with study drug

[40] - Subjects in ITT-A with at least one dose of prophylaxis treatment with study drug

[41] - Subjects in ITT-B with at least one dose of prophylaxis treatment with study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of FVIII in infusions for the treatment of bleeds

End point title	Consumption of FVIII in infusions for the treatment of bleeds[42]

End point description:

Factor VIII (FVIII) usage/consumption was summarized for infusions used to treat breakthrough bleeds. Consumption per subject's body weight per year was calculated and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[42] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[43]	11[44]	35[45]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	457.07 (± 526.87)	391.64 (± 219.61)	835.4 (± 1926.4)	

Notes:

[43] - Subjects in ITT-A with at least one bleed treated with study drug

[44] - Subjects in ITT-A with at least one bleed treated with study drug

[45] - Subjects in ITT-B with at least one bleed treated with study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions per bleed

End point title	Number of infusions per bleed[46]

End point description:

The number of infusions used to treat a bleed was defined as the first infusion to treat the bleed plus all follow-up infusions to treat the same bleed, if any. The mean value of number of infusions for each bleed was calculated and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[46] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[47]	13[48]	37[49]	
Units: infusions				
arithmetic mean (standard deviation)	1.3 (± 1.8)	1.4 (± 1.7)	1.7 (± 8.7)	

Notes:

[47] - Subjects in ITT-A with at least one bleed

[48] - Subjects in ITT-A with at least one bleed

[49] - Subjects in ITT-B with at least one bleed

Statistical analyses

No statistical analyses for this end point

Secondary: Response to treatment of bleeds

End point title	Response to treatment of bleeds[50]

End point description:

Subjects or caregivers were asked to assess the response to treatment of bleeds as excellent, good, moderate or poor. Percentage of bleeds per assessment was summarized and reported.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days (EDs) (median 73 EDs; median 6 months); Part B: at least 50 EDs or until inhibitor development (median 46 EDs; median 8 months)

Notes:

[50] - 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: The main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 therefore efficacy data for extension study is not presented. (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients)

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[51]	13[52]	37[53]	
Units: percentage of bleeds				
number (not applicable)				
Excellent	45.5	32.4	25.7	
Good	52.3	48.6	53.3	
Moderate	0.0	18.9	15.2	
Poor	2.3	0.0	5.7	

Notes:

[51] - Subjects in ITT-A with at least one bleed; number of bleeds assessed for the response = 44

[52] - Subjects in ITT-A with at least one bleed; number of bleeds assessed for the response = 37

[53] - Subjects in ITT-B with at least one bleed; number of bleeds assessed for the response = 105

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of BAY81-8973 in plasma

End point title	Half-life (t1/2) of BAY81-8973 in plasma[54]

End point description:

Half-life (t1/2) of BAY81-8973 in plasma was measured. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. Occurrence of "±" in relation with coefficient of variation is auto-generated by the database.

End point type	Secondary

End point timeframe:

Pre-infusion and until 24 hours post infusion

Notes:

[54] - 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: Participation in the PK evaluations was optional. The PK result of main study - Part B was not summarized due to the limited number of collected samples. The PK result of extension study is not presented as the main objective of the extension study was to demonstrate long-term safety of BAY 81-8973 (note: extension study was a single study. It is artificially described in two arms for ease of reporting data for former part A and former part B patients).

End point values	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[55]	9[56]		
Units: hour(s)				
geometric mean (geometric coefficient of variation)	13.2 (± 39.7)	12.1 (± 16.3)		

Notes:

[55] - Subjects in PKS-A with evaluable data for this endpoint

[56] - Subjects in PKS-A with evaluable data for this endpoint

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: from the first BAY81-8973 infusion until 3 days after the last infusion; Part B: from the first BAY81-8973 infusion until 7 days after the last infusion; Extension: from start of extension until 3 days after the last infusion in extension study

Adverse event reporting additional description:

Part A: median 6 months; Part B: median 8 months; Extension: median 3.1 years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Main study - Part A: PTPs 0-<6 years

Reporting group description:

Previously treated patients (PTPs) aged below 6 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.

Reporting group title	Main study - Part A: PTPs 6-12 years

Reporting group description:

Previously treated patients (PTPs) aged 6 to 12 years received BAY81-8973 25-50 IU/kg at least 2x/week for 6 months and at least 50 exposure days (EDs) in main study - Part A.

Reporting group title	Main study - Part B: PUPs/MTPs 0-<6 years

Reporting group description:

Previously untreated patients (PUPs) or minimally treated patients (MTPs, patients who had no more than 3 exposure days (EDs) with any FVIII product) received BAY81-8973 15-50 IU/kg at least 1x/week for at least 50 EDs or until inhibitor development in main study - Part B.

Reporting group title	Extension study - former Part A subjects

Reporting group description:

Subjects having reached at least 50 exposure days (EDs) in main study - Part A were offered participation in an open label extension study (optional). Subjects who transitioned from main study - Part A to the extension study received BAY81-8973, 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part A and extension study).

Reporting group title	Extension study - former Part B subjects

Reporting group description:

Subjects having reached at least 50 exposure days (EDs) in main study - Part B were offered participation in an open label extension study and received BAY81-8973 25-50 IU/kg at least 2x/week for at least 100 cumulative EDs (main study - Part B and extension study); subjects who developed an inhibitor in main study - Part B were offered participation in open label extension study and received Immune Tolerance Induction (ITI) treatment with BAY81-8973 until successful eradication of the inhibitor, or until failure, for approximately 18 months.

Serious adverse events	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	5 / 26 (19.23%)	26 / 43 (60.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			

Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental cleaning			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Adenotonsillectomy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheter removal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune tolerance induction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Decreased activity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extravasation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site granuloma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site related reaction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Laryngeal haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal device exposed			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	22 / 43 (51.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	24 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation cardiac			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electroencephalogram abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Traumatic haemothorax			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalomalacia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Multiple sclerosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Factor VIII inhibition			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombocytopenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	3 / 43 (6.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis reactive			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Gastroenteritis staphylococcal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Viral infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (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
Appendicitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis orbital			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epidemic pleurodynia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulpitis dental			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension study - former Part A subjects	Extension study - former Part B subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 46 (50.00%)	14 / 36 (38.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	2 / 46 (4.35%)	4 / 36 (11.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental cleaning			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenotonsillectomy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheter removal			

subjects affected / exposed	1 / 46 (2.17%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune tolerance induction			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased activity			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site granuloma			

subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site related reaction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal haematoma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device failure			
subjects affected / exposed	1 / 46 (2.17%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Internal device exposed			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electroencephalogram abnormal			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (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			
Craniocerebral injury			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth injury			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (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			
Cerebral haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomalacia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			

subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Factor VIII inhibition			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			

subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 46 (2.17%)	3 / 36 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	1 / 46 (2.17%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis reactive			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (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			
Bacterial infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis staphylococcal			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (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 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidemic pleurodynia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			

subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	2 / 46 (4.35%)	3 / 36 (8.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic syndrome			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Main study - Part A: PTPs 0-<6 years	Main study - Part A: PTPs 6-12 years	Main study - Part B: PUPs/MTPs 0-<6 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)	19 / 26 (73.08%)	28 / 43 (65.12%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	0 / 43 (0.00%)
occurrences (all)	0	3	0

Central venous catheter removal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Hyperthermia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Infusion site swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	5 / 25 (20.00%)	2 / 26 (7.69%)	12 / 43 (27.91%)
occurrences (all)	10	2	19
Catheter site haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 25 (8.00%)	4 / 26 (15.38%)	1 / 43 (2.33%)
occurrences (all)	4	4	1
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Productive cough			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	3	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Adenoidal hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Increased upper airway secretion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Product issues			

Device failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	3	0	1
Face injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Genital contusion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Lip injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Skin injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Subcutaneous haematoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Tongue injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Eye contusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ulna fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 25 (8.00%)	4 / 26 (15.38%)	0 / 43 (0.00%)
occurrences (all)	3	4	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Blood loss anaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Iron deficiency anaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Strabismus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1

Dental caries			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	6 / 43 (13.95%)
occurrences (all)	3	2	8
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	2	1
Glossodynia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Teething			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	4 / 43 (9.30%)
occurrences (all)	1	1	8
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 25 (12.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	3	0	0
Rash			

subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Ecchymosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Joint swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Synovitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	4
Bronchitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			

subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	3 / 43 (6.98%)
occurrences (all)	2	0	3
Cystitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Ear infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Gastrointestinal viral infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Hookworm infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	4 / 43 (9.30%)
occurrences (all)	0	1	4
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	6 / 43 (13.95%)
occurrences (all)	3	2	16
Oral herpes			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	3
Otitis media acute			

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	3 / 43 (6.98%)
occurrences (all)	1	1	4
Tonsillitis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	2	1	1
Tooth abscess			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Tracheitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	3 / 43 (6.98%)
occurrences (all)	1	2	3
Varicella			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Vascular device infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	1 / 43 (2.33%)
occurrences (all)	3	2	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Catheter site infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dysentery			

subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Enterovirus infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Extension study - former Part A subjects	Extension study - former Part B subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 46 (89.13%)	24 / 36 (66.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	5	0	

Central venous catheter removal			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Hyperthermia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Infusion site swelling			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Injection site bruising			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	3 / 46 (6.52%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Pyrexia			
subjects affected / exposed	8 / 46 (17.39%)	11 / 36 (30.56%)	
occurrences (all)	19	21	
Catheter site haematoma			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 46 (19.57%)	3 / 36 (8.33%)	
occurrences (all)	18	6	
Oropharyngeal pain			
subjects affected / exposed	5 / 46 (10.87%)	0 / 36 (0.00%)	
occurrences (all)	8	0	
Productive cough			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	3 / 46 (6.52%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Asthma			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Adenoidal hypertrophy			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Rhinorrhoea			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Increased upper airway secretion			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Product issues			

Device failure			
subjects affected / exposed	3 / 46 (6.52%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Neutrophil count increased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
White blood cell count increased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Face injury			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Genital contusion			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Head injury			
subjects affected / exposed	1 / 46 (2.17%)	4 / 36 (11.11%)	
occurrences (all)	1	4	
Limb injury			
subjects affected / exposed	9 / 46 (19.57%)	1 / 36 (2.78%)	
occurrences (all)	11	1	
Lip injury			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Road traffic accident			

subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Skin injury			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Tongue injury			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Eye contusion			
subjects affected / exposed	2 / 46 (4.35%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Joint injury			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Procedural pain			
subjects affected / exposed	3 / 46 (6.52%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Ulna fracture			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			

Headache			
subjects affected / exposed	8 / 46 (17.39%)	0 / 36 (0.00%)	
occurrences (all)	23	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 46 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	10	
Blood loss anaemia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 46 (2.17%)	2 / 36 (5.56%)	
occurrences (all)	5	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Photophobia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Strabismus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 46 (10.87%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Abdominal pain upper			
subjects affected / exposed	5 / 46 (10.87%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Constipation			
subjects affected / exposed	1 / 46 (2.17%)	1 / 36 (2.78%)	
occurrences (all)	1	1	

Dental caries			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	5 / 46 (10.87%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Glossodynia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Haematochezia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Teething			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Toothache			
subjects affected / exposed	2 / 46 (4.35%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	4 / 46 (8.70%)	6 / 36 (16.67%)	
occurrences (all)	4	10	
Nausea			
subjects affected / exposed	3 / 46 (6.52%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Rash			

subjects affected / exposed	3 / 46 (6.52%)	1 / 36 (2.78%)	
occurrences (all)	3	3	
Ecchymosis			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Dermatitis atopic			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 46 (13.04%)	0 / 36 (0.00%)	
occurrences (all)	9	0	
Joint swelling			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	4 / 46 (8.70%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Synovitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Groin pain			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 46 (2.17%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	2 / 46 (4.35%)	3 / 36 (8.33%)	
occurrences (all)	4	5	
Conjunctivitis			

subjects affected / exposed	3 / 46 (6.52%)	2 / 36 (5.56%)	
occurrences (all)	4	3	
Cystitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	4 / 46 (8.70%)	1 / 36 (2.78%)	
occurrences (all)	4	4	
Gastroenteritis			
subjects affected / exposed	1 / 46 (2.17%)	3 / 36 (8.33%)	
occurrences (all)	1	5	
Gastroenteritis viral			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Hookworm infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 46 (4.35%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Nasopharyngitis			
subjects affected / exposed	13 / 46 (28.26%)	9 / 36 (25.00%)	
occurrences (all)	31	23	
Oral herpes			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Otitis media			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	
Otitis media acute			

subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Rhinitis			
subjects affected / exposed	6 / 46 (13.04%)	1 / 36 (2.78%)	
occurrences (all)	8	3	
Tonsillitis			
subjects affected / exposed	10 / 46 (21.74%)	0 / 36 (0.00%)	
occurrences (all)	25	0	
Tooth abscess			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Tracheitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	6 / 46 (13.04%)	2 / 36 (5.56%)	
occurrences (all)	11	2	
Varicella			
subjects affected / exposed	2 / 46 (4.35%)	4 / 36 (11.11%)	
occurrences (all)	2	4	
Vascular device infection			
subjects affected / exposed	1 / 46 (2.17%)	1 / 36 (2.78%)	
occurrences (all)	2	2	
Viral infection			
subjects affected / exposed	6 / 46 (13.04%)	2 / 36 (5.56%)	
occurrences (all)	15	4	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Catheter site infection			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Dysentery			

subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	4	
Enterovirus infection			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Laryngitis			
subjects affected / exposed	1 / 46 (2.17%)	3 / 36 (8.33%)	
occurrences (all)	1	4	
Pharyngitis			
subjects affected / exposed	3 / 46 (6.52%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 46 (4.35%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	5 / 46 (10.87%)	0 / 36 (0.00%)	
occurrences (all)	10	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Iron deficiency			
subjects affected / exposed	0 / 46 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2011	Amendment 1 implemented mainly an improved explanation of the staggered enrollment and the number of subjects to be enrolled, clarification of start of prophylaxis in PUPs, revision of pharmacokinetic (PK) sampling scheme in Part A, updated information on BAY81-8973, clarification of in- and exclusion criteria and measurements of vital signs.
03 September 2012	Amendment 3 implemented mainly that PK sampling was no longer limited to subjects in Part A, the number of subjects for Part B (PUPs) was increased to ≥25 and ≤50, revisions and clarifications, and further clarification of in- and exclusion criteria.
08 April 2014	Amendment 4 introduced an optional pharmacogenetic analysis and epitope mapping of samples from subjects confirmed positive for inhibitor antibodies.
19 February 2016	Amendment 6 implemented clarifications on inhibitor testing during the extension phase and on FVIII:C determinations at screening. Visits in Part B were no longer described in months but in EDs. Furthermore, the possibility to enroll MTPs in Part B was added to the protocol. Consequently, inhibitor evaluation was added at screening in Part B for MTPs only.
30 May 2017	Amendment 7 increased the number of subjects in Part B to an additional 25. A staggered approach for subject enrollment was introduced in Part B as a safety measure. 10 subjects were recruited first, and enrollment to the next cohort could only start after the previous 10 subjects had 20 EDs without safety concerns. Inclusion criterion regarding inhibitor testing for MTPs was clarified.
01 February 2019	Amendment 8 clarified MTP definition, the time in the extension study, and ITI management in the extension study. An additional analysis was added, to be carried out when all PUPs/MTPs completed Part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 December 2016	Enrollment in Part B was temporarily suspended in December 2016 to undertake a comprehensive evaluation of a cluster of inhibitor cases that occurred from June to December 2016. After endorsement from the Data Monitoring Committee (DMC), the enrollment was resumed under amendment 7.	13 June 2017

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the small number of subject per group, all presented summary measures have to be evaluated with caution. If displayed standard deviation should be taken into account. The 3-year long term follow-up duration mentioned above is median duration.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26931631

http://www.ncbi.nlm.nih.gov/pubmed/26663410

http://www.ncbi.nlm.nih.gov/pubmed/27577234

http://www.ncbi.nlm.nih.gov/pubmed/25952661

http://www.ncbi.nlm.nih.gov/pubmed/27436242

http://www.ncbi.nlm.nih.gov/pubmed/28220555

http://www.ncbi.nlm.nih.gov/pubmed/30013766

http://www.ncbi.nlm.nih.gov/pubmed/32197139