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	

Results information

Result version number	v1
This version publication date	22 March 2020
First version publication date	22 March 2020

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	Interim
Date of interim/final analysis	10 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2019
Global end of trial reached?	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 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, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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	Italy: 11
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:

Study Part A was conducted at multiple centers in 12 countries between 09-JUN-2011 (first subject first visit) and 02-JAN-2013 (last subject last visit); Study Part B was conducted at multiple centers in 15 countries between 19-SEP-2012 (first subject first visit) and 09-SEP-2019 (last subject last visit).

Pre-assignment

Screening details:

Overall, 58 subjects were screened in Part A, of which 7 subjects were screening failures and 51 subjects - received at least one dose of the study drug; 52 subjects were screened in Part B, of which 9 subjects were screening failures and 43 subjects received at least one dose of the study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	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 (ED)

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 exposure days (ED), intravenous (IV) infusion

Arm title	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 (ED)

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 exposure days (ED), intravenous (IV) infusion

Arm title	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 50 EDs

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, 50 exposure days (ED), intravenous (IV) infusion

Number of subjects in period 1	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	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
Inhibitor management	-	-	17
Adverse event	-	-	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	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 (ED)	
Reporting group title	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 (ED)	
Reporting group title	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 50 EDs	

Reporting group values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years
Number of subjects	25	26	43
Age categorical Units: Subjects			
0- <6 years	25	0	43
6- 12 years	0	26	0
Age continuous Units: years			
arithmetic mean	3.8	8.8	0.8
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	Total		
Number of subjects	94		
Age categorical Units: Subjects			
0- <6 years	68		

6- 12 years	26		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	0		
Male	94		
Race Units: Subjects			
White	85		
Black	4		
American Indian or Alaska native	1		
White, American Indian or Alaska native	1		
Not reported	3		
Ethnicity Units: Subjects			
Not Hispanic or Latino	82		
Hispanic or Latino	10		
Not reported	2		

End points

End points reporting groups

Reporting group title	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 (ED)	
Reporting group title	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 (ED)	
Reporting group title	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 50 EDs	
Subject analysis set title	Safety analysis set (SAF) - A
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who entered 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 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 Study Part A and received at least one infusion of study medication with evaluable pharmacokinetic (PK) data.	

Primary: Annualized number of total bleeds within 48 h

End point title	Annualized number of total bleeds within 48 h[1]
End point description:	
Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds and 'other' bleeds) that occurred within 48 hours after all prophylaxis infusions was summarized and reported. '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.

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[2]	26[3]	43[4]	
Units: bleed(s)				
arithmetic mean (standard deviation)	2.23 (± 2.77)	1.86 (± 3.08)	1.9 (± 3.3)	

Notes:

[2] - ITT-A

[3] - ITT-A

[4] - 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[5]

End point description:

Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds and 'other' bleeds) that occurred within 48 hours after all prophylaxis infusions were summarized and reported. 'Other' bleeds were infusions with reason given as 'other'.

End point type	Primary

End point timeframe:

Within 48 hours post infusion

Notes:

[5] - 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.

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[6]	26[7]	43[8]	
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:

[6] - ITT-A

[7] - ITT-A

[8] - 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

End point description:

Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds and 'other' bleeds) that occurred during prophylaxis treatment was summarized and reported.. '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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[9]	26[10]	43[11]	
Units: bleed(s)				
arithmetic mean (standard deviation)	4.16 (± 5.02)	3.37 (± 5.01)	7.1 (± 8.6)	

Notes:

[9] - ITT-A

[10] - ITT-A

[11] - 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

End point description:

Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds and 'other' bleeds) that occurred during prophylaxis treatment were summarized and reported. '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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	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)				
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:

[12] - ITT-A

[13] - ITT-A

[14] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[15]	1[16]	5[17]	
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:

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

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

[17] - 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

End point title	Number of subjects with inhibitor development

End point description:

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

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[18]	26[19]	43[20]	
Units: subject(s)				
Low titer inhibitor	0	0	6	
High titer inhibitor	0	0	17	

Notes:

[18] - SAF-A

[19] - SAF-A

[20] - SAF-B

Statistical analyses

No statistical analyses for this end point

Secondary: Factor VIII recovery values

End point title	Factor VIII recovery values

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.

End point type	Secondary

End point timeframe:

Part A: 6 months and at least 50 exposure days; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[21]	26[22]	32[23]	
Units: kilogram(s)/deciliter				
arithmetic mean (standard deviation)	1.63 (± 0.31)	1.72 (± 0.46)	1.17 (± 0.82)	

Notes:

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

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

[23] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[24]	26[25]	43[26]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	5499.1 (± 1996.2)	4679.1 (± 1688.7)	2195.8 (± 1903.6)	

Notes:

[24] - ITT-A

[25] - ITT-A

[26] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[27]	26[28]	42[29]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	5224.8 (± 1760.2)	4492.7 (± 1667.6)	1486.6 (± 963.3)	

Notes:

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

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

[29] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[30]	11[31]	35[32]	
Units: international unit(s)/kilogram/year				
arithmetic mean (standard deviation)	457.07 (± 526.87)	391.64 (± 219.61)	835.4 (± 1926.4)	

Notes:

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

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

[32] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[33]	13[34]	37[35]	
Units: infusions				
arithmetic mean (standard deviation)	1.3 (± 1.8)	1.4 (± 1.7)	1.7 (± 8.7)	

Notes:

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

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

[35] - 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

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; Part B: 50 exposure days

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years	Part B: PUPs/MTPs 0-<6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[36]	13[37]	37[38]	
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:

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

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

[38] - 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[39]

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:

[39] - 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: PK analysis is only displayed for Part A. The summary of PK values in Part B will be presented in the final report for the extension study due to the limited number of collected samples.

End point values	Part A: PTPs 0-<6 years	Part A: PTPs 6-12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[40]	9[41]		
Units: hour(s)				
geometric mean (geometric coefficient of variation)	13.2 (± 39.7)	12.1 (± 16.3)		

Notes:

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

[41] - 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 and up to 3 days after the last infusion; Part B: from the first BAY81-8973 infusion and up to 7 days after the last infusion	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	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 (ED).	
Reporting group title	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 50 EDs.	
Reporting group title	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 (ED).	

Serious adverse events	Part A: PTPs 0-<6 years	Part B: PUPs/MTPs 0-<6 years	Part A: PTPs 6-12 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	26 / 43 (60.47%)	5 / 26 (19.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	0 / 25 (0.00%)	22 / 43 (51.16%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	24 / 24	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%)	1 / 43 (2.33%)	0 / 26 (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
Mouth injury			

subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Dental cleaning			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Encephalomalacia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Factor VIII inhibition			

subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	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%)	1 / 43 (2.33%)	0 / 26 (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
Decreased activity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Extravasation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Facial pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Musculoskeletal and connective tissue disorders			
Haemarthrosis			

subjects affected / exposed	0 / 25 (0.00%)	3 / 43 (6.98%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Soft tissue haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	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%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
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 staphylococcal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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 viral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	0 / 26 (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
Tooth abscess			

subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A: PTPs 0-<6 years	Part B: PUPs/MTPs 0-<6 years	Part A: PTPs 6-12 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 25 (68.00%)	27 / 43 (62.79%)	19 / 26 (73.08%)
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Hyperthermia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Infusion site swelling			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Injection site bruising			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Pyrexia			

subjects affected / exposed	5 / 25 (20.00%)	12 / 43 (27.91%)	2 / 26 (7.69%)
occurrences (all)	10	19	2
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 25 (8.00%)	1 / 43 (2.33%)	4 / 26 (15.38%)
occurrences (all)	4	1	4
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	3
Productive cough			
subjects affected / exposed	2 / 25 (8.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 25 (8.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences (all)	3	1	0
Face injury			

subjects affected / exposed	0 / 25 (0.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 25 (0.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Genital contusion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	1 / 25 (4.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Limb injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Lip injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Skin injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	1 / 25 (4.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Subcutaneous haematoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Tongue injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

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

Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	6 / 43 (13.95%)	1 / 26 (3.85%)
occurrences (all)	3	8	2
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	2
Glossodynia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Teething			
subjects affected / exposed	0 / 25 (0.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	4 / 43 (9.30%)	1 / 26 (3.85%)
occurrences (all)	1	8	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 25 (12.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	0 / 25 (0.00%)	3 / 43 (6.98%)	2 / 26 (7.69%)
occurrences (all)	0	3	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Joint swelling			

subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Synovitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences (all)	0	4	0
Bronchitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	2 / 25 (8.00%)	3 / 43 (6.98%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Cystitis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 43 (2.33%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Ear infection			
subjects affected / exposed	1 / 25 (4.00%)	2 / 43 (4.65%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	3 / 43 (6.98%)	0 / 26 (0.00%)
occurrences (all)	0	3	0

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

Tracheitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	3 / 43 (6.98%)	1 / 26 (3.85%)
occurrences (all)	1	3	2
Varicella			
subjects affected / exposed	0 / 25 (0.00%)	1 / 43 (2.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Vascular device infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 43 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	3 / 25 (12.00%)	1 / 43 (2.33%)	2 / 26 (7.69%)
occurrences (all)	3	1	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 43 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1

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 reporting group, all presented summary measures (e.g. mean and proportion) have to be evaluated with caution. If displayed standard deviation should be taken into account.

Notes: