



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 | v2 |
| This version publication date | 10 May 2021 |
| First version publication date | 22 March 2020 |
| Version creation reason | |

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) | EMA-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 | 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:

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] | 43 ^[26] | |
| Units: subject(s) | | | | |
| Low titer inhibitor | 0 | 0 | 6 | |
| High titer inhibitor | 0 | 0 | 17 | |

Notes:

[24] - SAF-A

[25] - SAF-A

[26] - SAF-B

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 (\pm 1996.2) | 4679.1 (\pm 1688.7) | 2195.8 (\pm 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 (\pm 1760.2) | 4492.7 (\pm 1667.6) | 1486.6 (\pm 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

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 occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Hyperthermia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Infusion site swelling subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Injection site bruising subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 10 | 2 / 26 (7.69%) 2 | 12 / 43 (27.91%) 19 |
| Catheter site haematoma subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Immune system disorders | | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Perineal pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 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 occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Investigations | | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 26 (0.00%) 0 | 1 / 43 (2.33%) 1 |
| Face injury subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 43 (4.65%) 2 |
| Fall subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 43 (4.65%) 2 |
| Genital contusion subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Head injury subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 1 / 43 (2.33%) 1 |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Lip injury subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 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 occurrences (all) | 2 / 25 (8.00%) 3 | 4 / 26 (15.38%) 4 | 0 / 43 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 3 | 3 / 43 (6.98%) 3 |
| Blood loss anaemia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 43 (4.65%) 2 |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 43 (2.33%) 1 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 43 (2.33%) 1 |
| Eye disorders | | | |
| Conjunctivitis allergic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Photophobia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Strabismus subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 3 | 0 / 43 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 43 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 43 (2.33%) 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 occurrences (all) | 2 / 46 (4.35%) 2 | 0 / 36 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Hyperthermia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Infusion site swelling subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Injection site bruising subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 4 | 0 / 36 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 8 / 46 (17.39%) 19 | 11 / 36 (30.56%) 21 | |
| Catheter site haematoma subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 2 / 36 (5.56%) 3 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 0 / 36 (0.00%) 0 | |
| Immune system disorders | | | |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Reproductive system and breast disorders | | | |
| Perineal pain subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 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 occurrences (all) | 3 / 46 (6.52%) 3 | 0 / 36 (0.00%) 0 | |
| Investigations | | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 0 / 36 (0.00%) 0 | |
| Face injury subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 36 (2.78%) 1 | |
| Fall subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | 0 / 36 (0.00%) 0 | |
| Genital contusion subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Head injury subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 4 / 36 (11.11%) 4 | |
| Limb injury subjects affected / exposed occurrences (all) | 9 / 46 (19.57%) 11 | 1 / 36 (2.78%) 1 | |
| Lip injury subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 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 occurrences (all) | 8 / 46 (17.39%) 23 | 0 / 36 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 3 / 36 (8.33%) 10 | |
| Blood loss anaemia subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 36 (0.00%) 0 | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 5 | 2 / 36 (5.56%) 2 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 2 / 36 (5.56%) 2 | |
| Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Photophobia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Strabismus subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 5 / 46 (10.87%) 5 | 0 / 36 (0.00%) 0 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 46 (10.87%) 5 | 0 / 36 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 1 / 36 (2.78%) 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>