



Clinical trial results:

A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY94-9027 in Severe Hemophilia A

Summary

| | |
|--------------------------|--|
| EudraCT number | 2011-005210-11 |
| Trial protocol | GB BE NL NO AT DE DK PL FR IT Outside EU/EEA |
| Global end of trial date | |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 |
| This version publication date | 21 November 2018 |
| First version publication date | 15 April 2016 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY94-9027/13024 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01580293 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany, |
| 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-001229-PIP01-11 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 08 September 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 June 2014 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

1. Part A main study: To assess the efficacy of BAY94-9027 in prevention and treatment of bleeding at different infusion schedules 2. Part A Optional Extension: To assess the long term safety of BAY94-9027 over at least 100 accumulated exposure days (ED) (main study plus extension) 3. Part B main study and extension: To assess the safety and efficacy of BAY94-9027 in the prevention of bleeding during major surgical procedures

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. 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 | 23 April 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Colombia: 5 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Israel: 16 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Japan: 11 |
| Country: Number of subjects enrolled | Korea, Republic of: 8 |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Country: Number of subjects enrolled | Norway: 3 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Singapore: 9 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Turkey: 5 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | United States: 30 |
| Country: Number of subjects enrolled | Romania: 2 |
| Worldwide total number of subjects | 145 |
| EEA total number of subjects | 55 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 14 |
| Adults (18-64 years) | 131 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 parts: Part A (main study [36-week treatment period] and an optional extension [a minimum of 6 months and at least 100 total exposure days, or until marketing authorization of the drug]) and Part B (main study [up to 3 weeks] and extension [until the end of Part A extension]).

Pre-assignment

Screening details:

Of 149 subjects screened in Part A, 134 were treated and the reasons for non-inclusion of 15 patients were screen failure, consent withdrawal, and non-adherence to protocol visit windows. A total of 16 subjects (including 5 subjects from Part A) were enrolled and treated in Part B.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Part A |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | BAY94-9027 On-demand Treatment – Part A |

Arm description:

On-demand treatment with BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 international units per kilogram [IU/kg]).

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Damoctocog alfa pegol |
| Investigational medicinal product code | BAY94-9027 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

On-demand treatment with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg).

| | |
|------------------|---|
| Arm title | BAY94-9027 Prophylaxis Treatment – Part A |
|------------------|---|

Arm description:

All subjects in the prophylaxis arms started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than (<) 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Damoctocog alfa pegol |
| Investigational medicinal product code | BAY94-9027 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

All subjects in the prophylaxis arms started with BAY94-9027 IV infusion over a period of 1 to 15 minutes, 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects

who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

| Number of subjects in period 1 | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A |
|---------------------------------------|---|---|
| Started | 20 | 114 |
| Completed | 18 | 108 |
| Not completed | 2 | 6 |
| Consent withdrawn by subject | 1 | 4 |
| Adverse event, non-fatal | - | 2 |
| Unspecified | 1 | - |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Part B |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---|
| Arm title | BAY949027 Treatment in Major Surgery - Part B |
|------------------|---|

Arm description:

This reporting group included subjects who were treated in Part A and continued treatment in Part B, and subjects who were treated in Part B only. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Damoctocog alfa pegol |
| Investigational medicinal product code | BAY94-9027 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

| | |
|---|--|
| Number of subjects in period 2^[1] | BAY949027 Treatment in Major Surgery - Part B |
| Started | 16 |
| Completed | 14 |
| Not completed | 2 |
| Dropped-out | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Period 3

| | |
|------------------------------|--------------------|
| Period 3 title | Baseline period |
| Is this the baseline period? | Yes ^[2] |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | BAY94-9027 Treatment - Part A |

Arm description:

This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Damoctocog alfa pegol |
| Investigational medicinal product code | BAY94-9027 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BAY94-9027 as an IV infusion over a period of 1 to 15 minutes, and the dosage schedule as follows: On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

| | |
|------------------|---|
| Arm title | BAY94-9027 Treatment in Major surgery - Part B Only |
|------------------|---|

Arm description:

This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and

for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Damoctocog alfa pegol |
| Investigational medicinal product code | BAY94-9027 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This study was conducted in 2 parts, Part A and Part B. Hence, following periods (Parts A and B), a separate baseline period combining all the arms under Parts A and B, was created to report baseline characteristics.

| Number of subjects in period 3 | BAY94-9027 Treatment - Part A | BAY94-9027 Treatment in Major surgery - Part B Only |
|--------------------------------|----------------------------------|---|
| | | |
| Started | 134 | 11 |
| Completed | 126 | 10 |
| Not completed | 8 | 1 |
| Consent withdrawn by subject | 5 | - |
| Adverse event, non-fatal | 2 | - |
| Unspecified | 1 | - |
| Dropped-out | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | BAY94-9027 Treatment - Part A |
|-----------------------|-------------------------------|

Reporting group description:

This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

| | |
|-----------------------|---|
| Reporting group title | BAY94-9027 Treatment in Major surgery - Part B Only |
|-----------------------|---|

Reporting group description:

This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

| Reporting group values | BAY94-9027 Treatment - Part A | BAY94-9027 Treatment in Major surgery - Part B Only | Total |
|---|----------------------------------|---|-------|
| Number of subjects | 134 | 11 | 145 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 35.9 ± 13.5 | 37.9 ± 13.7 | - |
| Gender categorical Units: Subjects | | | |
| Male | 134 | 11 | 145 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | BAY94-9027 On-demand Treatment – Part A |
| Reporting group description: On-demand treatment with BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 international units per kilogram [IU/kg]). | |
| Reporting group title | BAY94-9027 Prophylaxis Treatment – Part A |
| Reporting group description: All subjects in the prophylaxis arms started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than (<) 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group). | |
| Reporting group title | BAY949027 Treatment in Major Surgery - Part B |
| Reporting group description: This reporting group included subjects who were treated in Part A and continued treatment in Part B, and subjects who were treated in Part B only. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response. | |
| Reporting group title | BAY94-9027 Treatment - Part A |
| Reporting group description: This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group). | |
| Reporting group title | BAY94-9027 Treatment in Major surgery - Part B Only |
| Reporting group description: This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response. | |
| Subject analysis set title | Part A Intent-To-Treat (ITT) Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Part A ITT population (N=132) included all the subjects who were enrolled into Part A of the study and received at least 1 dose of the study medication during Part A, and has subsequent infusion for either prophylaxis or bleed. | |
| Subject analysis set title | Part B Intent-To-Treat (ITT) Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Part B ITT population (N=14) included all the subjects who were enrolled into Part B of the study, received at least 1 dose of the study medication during Part B, and had undergone surgery. | |
| Subject analysis set title | Part B Safety Population |

| | |
|--|--|
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Part B Safety population (N=16) included all subjects who received at least 1 dose of study drug during Part B of the study. | |
| Subject analysis set title | Pharmacokinetic Analysis Set (PKS) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: PKS (N=22) included all subjects with a valid profile of BAY94-9027 during Part A of the study. | |
| Subject analysis set title | BAY94-9027 Treatment – Part A, Week 36 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: This reporting group (N=15) included all PKS subjects treated with multiple doses (last dose paired) of BAY94-9027 as an IV infusion over 10 minutes at Week 36. Paired data were defined as the single dose data for the sub-set of subjects who also had multiple dose PK data. | |
| Subject analysis set title | BAY94-9027 Treatment – Part A, Week 0 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: This reporting group (N=22) included all PKS subjects treated with a single (first) dose of BAY94-9027 as an IV infusion over 10 minutes at Week 0. | |
| Subject analysis set title | Part A Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Part A Safety population (N=134) included all subjects who received at least 1 dose of study drug during Part A of the study. | |

Primary: Annualized Number of Total Bleeds in On-demand Treatment arm (Weeks 0 -36) and Prophylaxis arm (Weeks 10 - 36, excluding rescue bleeds) – Part A

| | |
|--|---|
| End point title | Annualized Number of Total Bleeds in On-demand Treatment arm (Weeks 0 -36) and Prophylaxis arm (Weeks 10 - 36, excluding rescue bleeds) – Part A ^[1] |
| End point description: Annualized number of total bleeds was defined as the annualized sum of spontaneous bleeds and trauma bleeds. | |
| End point type | Primary |
| End point timeframe: On-demand: Weeks 0 -36 and Prophylaxis: Weeks 10 - 36 during Part A | |

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[2] | 110 ^[3] | | |
| Units: bleeds | | | | |
| median (full range (min-max)) | 23.42 (7.3 to 83.2) | 2.09 (0 to 53.1) | | |

Notes:

[2] - Part A ITT population

[3] - Part A ITT population with evaluable subjects for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Assessment of Adequacy of Hemostasis in Major Surgery – Part B

| | |
|-----------------|--|
| End point title | Physician's Assessment of Adequacy of Hemostasis in Major Surgery – Part B |
|-----------------|--|

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. Adequacy of hemostasis was assessed as excellent, good, moderate or poor, by the Physician during Part B of the study. No subjects were assessed as moderate or poor.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 6 weeks during Part B

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[4] | | | |
| Units: Number of surgeries | | | | |
| Good | 10 | | | |
| Excellent | 7 | | | |

Notes:

[4] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions for Major Surgery – Part B

| | |
|-----------------|--|
| End point title | Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions for Major Surgery – Part B |
|-----------------|--|

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 6 weeks during Part B

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[5] | | | |
| Units: infusions | | | | |
| median (full range (min-max)) | 8 (2 to 37) | | | |

Notes:

[5] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion for Major Surgery – Part B

| | |
|-----------------|---|
| End point title | Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion for Major Surgery – Part B |
|-----------------|---|

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. Total dose per kilogram per Infusion was expressed in international units per kilogram per infusion (IU/kg/infusion).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 6 weeks during Part B

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[6] | | | |
| Units: IU/kg/infusion | | | | |
| median (full range (min-max)) | 34 (26 to 51) | | | |

Notes:

[6] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Assessment of Response to Treatment - Part B

| | |
|-----------------|---|
| End point title | Investigator's Assessment of Response to Treatment - Part B |
|-----------------|---|

End point description:

Subject's response to treatment was assessed by Investigator as excellent, good, moderate, poor or missing during Part B of the study. No subjects were assessed as poor.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 6 weeks during Part B

| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[7] | | | |
| Units: Number of surgeries | | | | |
| Excellent | 8 | | | |
| Good | 5 | | | |
| Moderate | 3 | | | |
| Missing | 1 | | | |

Notes:

[7] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Assessment of Response to Treatment of a Bleed – Part A

| | |
|-----------------|---|
| End point title | Subject's Assessment of Response to Treatment of a Bleed – Part A |
|-----------------|---|

End point description:

Adequacy of hemostasis was assessed by subject as excellent, good, moderate, poor or missing during Part A of the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 to 36 during Part A

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[8] | 112 ^[9] | | |
| Units: bleeds | | | | |
| Excellent or Good | 252 | 256 | | |
| Missing | 3 | 6 | | |
| Excellent | 81 | 107 | | |
| Good | 171 | 149 | | |
| Moderate | 115 | 47 | | |
| Poor | 16 | 7 | | |

Notes:

[8] - Part A ITT population

[9] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Developed Human Coagulation Factor VIII (FVIII) Inhibitor – Part A

| | |
|-----------------|---|
| End point title | Number of Subjects Developed Human Coagulation Factor VIII (FVIII) Inhibitor – Part A |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 to 36 during Part A

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[10] | 114 ^[11] | | |
| Units: Subjects | 0 | 0 | | |

Notes:

[10] - Part A Safety population

[11] - Part A Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Overall Pain Severity and Interference due to Pain at Week 36 – Part A

| | |
|-----------------|--|
| End point title | Change From Baseline in Overall Pain Severity and Interference due to Pain at Week 36 – Part A |
|-----------------|--|

End point description:

Brief Pain Inventor (BPI) – Short Form (BPI-SF) was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess pain. BPI-SF was typically scored by averaging the pain severity score and overall pain interference score. Scores ranged from 0 to 10 and a higher score indicates a higher level of pain/interference. Mean change from baseline was reported in the below table. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 (baseline) and Week 36 during Part A

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[12] | 112 ^[13] | | |
| Units: scores on a scale | | | | |

| | | | | |
|------------------------------------|-------|-------|--|--|
| number (not applicable) | | | | |
| Pain severity subscale (N= 15, 83) | -0.8 | 0.1 | | |
| Interference subscale (N=15, 85) | -0.99 | -0.06 | | |

Notes:

[12] - Part A ITT population

[13] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire at Week 36 – Part A

| | |
|-----------------|--|
| End point title | Change From Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire at Week 36 – Part A |
|-----------------|--|

End point description:

The WPAI is a validated instrument to assess the effect of hemophilia on ability to work, attend classes, and perform regular daily activities in subjects aged 12 and above. The WPAI also contained classroom impairment questions (CIQ). The questionnaire was self-administered and comprised of nine questions that elicited information on work, classroom, and daily activity impairment during the previous seven days. WPAI outcomes that are overall work and activity impairment, transformed to impairment percentages (range from 0 to 100), with higher numbers indicating greater impairment and less productivity. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 (baseline) and Week 36 during Part A

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[14] | 112 ^[15] | | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Activity impairment (N= 19,108) | 4.74 (± 24.12) | -7.13 (± 20) | | |
| Overall work impairment (N= 12,62) | 4.44 (± 21.94) | -1.22 (± 21.94) | | |

Notes:

[14] - Part A ITT population

[15] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life by Hemophilia Specific Quality of Life for Adults (Haemo-QoL-A) Overall Score at Week 36 – Part A

| | |
|-----------------|---|
| End point title | Change From Baseline in Quality of Life by Hemophilia Specific Quality of Life for Adults (Haemo-QoL-A) Overall Score at Week 36 – Part A |
|-----------------|---|

End point description:

Quality of life (QoL) was measured by the Haemo-QoL-A overall score, which ranged from 0 (the best

condition) to 100 (the worst condition).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 0 (baseline) and Week 36 during Part A | |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 ^[16] | 97 ^[17] | | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | -0.14 (± 9.7) | 2.59 (± 7.98) | | |

Notes:

[16] - Part A ITT population with subjects evaluable for this outcome

[17] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Drug Plasma Concentration (Cmax) Following Single and Multiple Doses of BAY94-9027 – Part A

| | |
|-----------------|---|
| End point title | Maximum Drug Plasma Concentration (Cmax) Following Single and Multiple Doses of BAY94-9027 – Part A |
|-----------------|---|

End point description:

Maximum observed drug concentration, directly taken from analytical data. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. Cmax was expressed in international Units per deciliter (IU/dL).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

| | | | | |
|---|---|---|--|--|
| End point values | BAY94-9027 Treatment – Part A, Week 36 | BAY94-9027 Treatment – Part A, Week 0 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 ^[18] | 22 ^[19] | | |
| Units: IU/dL | | | | |
| geometric mean (geometric coefficient of variation) | 177.1 (± 20.98) | 162.8 (± 14.74) | | |

Notes:

[18] - PKS with subjects evaluable for this outcome

[19] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity (AUC) Following Single and Multiple Doses of BAY94-9027 – Part A

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity (AUC) Following Single and Multiple Doses of BAY94-9027 – Part A |
|-----------------|--|

End point description:

AUC=AUC(0-tlast)+Clast,calc/lambdaZ. AUC(0-tlast) is defined as AUC from time 0 to the last data point >lower limit of quantitation (LLOQ), calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule. Clast is the last concentration value above LLOQ, directly taken from analytical data. lambdaZ is the apparent terminal rate constant, calculated from the slope of a log-linear regression of the unweighted data considering the last concentration time points >LLOQ (3 IU/dL). AUC expressed in hour*IU/dL. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

| | | | | |
|---|--|---------------------------------------|--|--|
| End point values | BAY94-9027 Treatment – Part A, Week 36 | BAY94-9027 Treatment – Part A, Week 0 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 ^[20] | 22 ^[21] | | |
| Units: h*IU/dL | | | | |
| geometric mean (geometric coefficient of variation) | 4131 (± 28.8) | 3708 (± 33.77) | | |

Notes:

[20] - PKS with subjects evaluable for this outcome

[21] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t1/2) Following Single and Multiple Doses of BAY94-9027 – Part A

| | |
|-----------------|--|
| End point title | Terminal Elimination Half Life (t1/2) Following Single and Multiple Doses of BAY94-9027 – Part A |
|-----------------|--|

End point description:

t1/2=ln2/ lambdaZ. lambdaZ is the apparent terminal rate constant, calculated from the slope of a log-linear regression of the unweighted data considering the last concentration time points >LLOQ (3 IU/dL). Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

| End point values | BAY94-9027 Treatment – Part A, Week 36 | BAY94-9027 Treatment – Part A, Week 0 | | |
|---|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 ^[22] | 22 ^[23] | | |
| Units: Hours | | | | |
| geometric mean (geometric coefficient of variation) | 19.6 (± 38.48) | 17.1 (± 27.05) | | |

Notes:

[22] - PKS with subjects evaluable for this outcome

[23] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Human Coagulation Factor VIII (FVIII) Recovery Value in Chromogenic Assay – Part A

| | |
|---|--|
| End point title | Overall Human Coagulation Factor VIII (FVIII) Recovery Value in Chromogenic Assay – Part A |
| End point description: | |
| Recovery was calculated by the following formula: Recovery = (post-infusion FVIII activity – pre-infusion FVIII activity) * weight / dose (in IU). | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0 to 36 during Part A | |

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[24] | 112 ^[25] | | |
| Units: Kilogram per deciliter | | | | |
| arithmetic mean (full range (min-max)) | 2.671 (1.87 to 3.85) | 2.675 (1.32 to 4.48) | | |

Notes:

[24] - Part A ITT population

[25] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Bleed Location – Part A

| | |
|---|-------------------------|
| End point title | Bleed Location – Part A |
| End point description: | |
| Bleed locations were categorised as joint, muscle, skin/mucosa, internal, others and missing. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0 to 36 during Part A | |

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[26] | 112 ^[27] | | |
| Units: bleeds | | | | |
| Missing | 0 | 0 | | |
| Joint | 303 | 235 | | |
| Muscle | 54 | 59 | | |
| Skin/Mucosa | 12 | 12 | | |
| Internal | 7 | 7 | | |
| Other | 26 | 16 | | |

Notes:

[26] - Part A ITT population

[27] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of Joint Bleeds, Trauma, Spontaneous Bleeds for Subjects in Prophylaxis arm- Part A

| | |
|-----------------|---|
| End point title | Annualized Number of Joint Bleeds, Trauma, Spontaneous Bleeds for Subjects in Prophylaxis arm- Part A |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 10 to 36

| End point values | BAY94-9027 Prophylaxis Treatment – Part A | | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[28] | | | |
| Units: bleeds | | | | |
| median (full range (min-max)) | | | | |
| Joint Bleeds | 1.93 (0 to 53.1) | | | |
| Trauma Bleeds | 0 (0 to 14.4) | | | |
| Spontaneous Bleeds | 0 (0 to 53.1) | | | |

Notes:

[28] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions– Part A

| | |
|------------------------|---|
| End point title | Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions– Part A |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0 to 36 | |

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[29] | 112 ^[30] | | |
| Units: infusions | | | | |
| median (full range (min-max)) | 29 (9 to 76) | 59 (4 to 101) | | |

Notes:

[29] - Part A ITT population

[30] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Year – Part A

| | |
|------------------------|---|
| End point title | Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Year – Part A |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0 to 36 | |

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[31] | 112 ^[32] | | |
| Units: IU/kg/year | | | | |
| median (full range (min-max)) | 1518.5 (390 to 3655) | 3255.7 (893 to 5915) | | |

Notes:

[31] - Part A ITT population

[32] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion - Part A

| | |
|-----------------|---|
| End point title | Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion - Part A |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 to 36 during Part A

| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[33] | 112 ^[34] | | |
| Units: IU/kg/infusion | | | | |
| median (full range (min-max)) | 32.8 (23 to 58) | 38.7 (25 to 48) | | |

Notes:

[33] - Part A ITT population

[34] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII(rFVIII) Usage Expressed as Total Dose per Kilogram In Subjects with Prophylaxis Treatment – Part A

| | |
|-----------------|--|
| End point title | Recombinant Human Factor VIII(rFVIII) Usage Expressed as Total Dose per Kilogram In Subjects with Prophylaxis Treatment – Part A |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 to 36 during Part A

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | BAY94-9027 Prophylaxis Treatment – Part A | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 112 ^[35] | | | |
| Units: IU/kg | | | | |
| median (full range (min-max)) | 2203.1 (100 to 2819) | | | |

Notes:

[35] - Part A ITT population treated for prophylaxis

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusions to Control the Bleed – Part A

| | |
|------------------------|---|
| End point title | Number of Infusions to Control the Bleed – Part A |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0 to 36 | |

| | | | | |
|--|--|--|--|--|
| End point values | BAY94-9027 On-demand Treatment – Part A | BAY94-9027 Prophylaxis Treatment – Part A | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[36] | 112 ^[37] | | |
| Units: bleeds | | | | |
| 1 infusion | 307 | 262 | | |
| 2 infusions | 45 | 22 | | |
| Greater than or equal to (>=) 3 infusions | 34 | 32 | | |

Notes:

[36] - Part A ITT population

[37] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds Over Time Since Previous Prophylaxis Infusion - Part A

| | |
|------------------------|--|
| End point title | Number of Bleeds Over Time Since Previous Prophylaxis Infusion - Part A |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Weeks 0 to 36

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | BAY94-9027 Prophylaxis Treatment – Part A | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[38] | | | |
| Units: bleeds | | | | |
| <1 day | 19 | | | |
| >=1 to <2 days | 27 | | | |
| >=2 to <3 days | 43 | | | |
| >=3 to <4 days | 42 | | | |
| >=4 to <5 days | 28 | | | |
| >=5 to <6 days | 33 | | | |
| >=6 to <7 days | 11 | | | |
| >=7 days | 3 | | | |

Notes:

[38] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Requiring Dose Escalation or Dose Increase During Weeks 10 to 36 – Part A

| | |
|-----------------|--|
| End point title | Number of Subjects Requiring Dose Escalation or Dose Increase During Weeks 10 to 36 – Part A ^[39] |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 10 to 36 during Part A

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed during Part A only and reported as planned.

| | | | | |
|-----------------------------|-------------------------------------|--|--|--|
| End point values | BAY94-9027 Treatment – Part A | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[40] | | | |
| Units: Subjects | | | | |
| Dose frequency increased | 11 | | | |
| Dose increased | 9 | | | |

Notes:

[40] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Assessment of Adequacy of Hemostasis During Minor Surgery – Part A

| | |
|-----------------|--|
| End point title | Physician's Assessment of Adequacy of Hemostasis During Minor Surgery – Part A ^[41] |
|-----------------|--|

End point description:

Minor surgery was defined as any surgical procedure that did not meet the definition of major, and included simple dental extractions, incision and drainage of abscesses, or simple excisions. A total of 17 minor surgeries performed in 10 subjects were reported during Part A of the study. Adequacy of hemostasis was assessed as excellent or good by the Physician during Part A of the study. The maximum blood loss during surgery was 100 mL during the draining of an abscess. No subjects required blood transfusions.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 0 to 36 during Part A

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed during Part A and Part B, however, Physician's Assessment of Adequacy of Hemostasis during Part B was reported as a separate endpoint.

| | | | | |
|-----------------------------|-------------------------------|--|--|--|
| End point values | BAY94-9027 Treatment - Part A | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 ^[42] | | | |
| Units: Number of surgeries | | | | |
| Excellent | 9 | | | |
| Good | 6 | | | |
| Missing | 2 | | | |

Notes:

[42] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Change/Drop in Hemoglobin/Hematocrit Laboratory Assessments – Part B

| | |
|-----------------|--|
| End point title | Number of Subjects With Change/Drop in Hemoglobin/Hematocrit Laboratory Assessments – Part B |
|-----------------|--|

End point description:

Hematocrit is defined as the volume percentage (%) of red blood cells in blood. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to 6 weeks during Part B

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[43] | | | |
| Units: Subjects | | | | |
| Hematocrit (N=11) | 3 | | | |
| Hemoglobin (N=11) | 2 | | | |

Notes:

[43] - Part B Safety population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Blood Loss in Major Surgery – Part B

| | |
|--|--|
| End point title | Maximum Blood Loss in Major Surgery – Part B |
| End point description: | |
| Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Baseline up to 6 weeks during Part B | |

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[44] | | | |
| Units: milliliter | | | | |
| number (not applicable) | | | | |
| During surgery | 1000 | | | |

Notes:

[44] - Part B ITT population with subjects treated for major surgery

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects who Took Anti-fibrinolytic Medications During Major Surgery – Part B

| | |
|--|---|
| End point title | Number of Subjects who Took Anti-fibrinolytic Medications During Major Surgery – Part B |
| End point description: Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. | |
| End point type | Other pre-specified |
| End point timeframe: Baseline up to 6 weeks during Part B | |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[45] | | | |
| Units: Subjects | 6 | | | |

Notes:

[45] - Part B ITT population with subjects treated for major surgery

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Units of Blood Transfused in Major Surgery – Part B

| | |
|--|---|
| End point title | Units of Blood Transfused in Major Surgery – Part B |
| End point description: Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. | |
| End point type | Other pre-specified |
| End point timeframe: Baseline up to 6 weeks during Part B | |

| | | | | |
|-------------------------------|---|--|--|--|
| End point values | BAY949027 Treatment in Major Surgery - Part B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 ^[46] | | | |
| Units: Milliliter | | | | |
| median (full range (min-max)) | 865 (600 to 1381.2) | | | |

Notes:

[46] - Part B ITT population who had blood transfusions during major surgery

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected after the first dose of study drug and up to 7 days after the last dose over a period of approximately two years

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | BAY94-9027 on-demand treatment - Part A |
|-----------------------|---|

Reporting group description:

Subjects in on-demand treatment received BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg (international units per kilogram)).

| | |
|-----------------------|--|
| Reporting group title | BAY94-9027 treatment in Major surgery - Part B |
|-----------------------|--|

Reporting group description:

Subjects who underwent major surgery received BAY 94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

| | |
|-----------------------|---|
| Reporting group title | BAY94-9027 prophylaxis treatment - Part A |
|-----------------------|---|

Reporting group description:

Subjects in prophylaxis treatment started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week forced group).

| Serious adverse events | BAY94-9027 on-demand treatment - Part A | BAY94-9027 treatment in Major surgery - Part B | BAY94-9027 prophylaxis treatment - Part A |
|---|---|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 2 / 16 (12.50%) | 9 / 114 (7.89%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Anti factor VIII antibody positive | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 16 (12.50%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonoscopy | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Knee arthroplasty | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device malfunction | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilic arthropathy | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Device related infection | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | BAY94-9027 on-demand treatment - Part A | BAY94-9027 treatment in Major surgery - Part B | BAY94-9027 prophylaxis treatment - Part A |
|---|---|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 20 (70.00%) | 12 / 16 (75.00%) | 61 / 114 (53.51%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 16 (12.50%) | 1 / 114 (0.88%) |
| occurrences (all) | 0 | 2 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 2 / 114 (1.75%) |
| occurrences (all) | 1 | 0 | 3 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|--|----------------------|----------------------|-----------------------|
| Injection site rash subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Local swelling subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 16 (12.50%) 2 | 0 / 114 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 0 / 16 (0.00%) 0 | 6 / 114 (5.26%) 8 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 1 / 114 (0.88%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 16 (0.00%) 0 | 8 / 114 (7.02%) 10 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 3 / 114 (2.63%) 3 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 2 | 0 / 16 (0.00%) 0 | 1 / 114 (0.88%) 1 |
| Blood magnesium decreased | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 16 (18.75%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Injury, poisoning and procedural complications | | | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 4 / 114 (3.51%) |
| occurrences (all) | 1 | 0 | 6 |
| Post procedural oedema | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 16 (18.75%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Procedural pain | | | |

| | | | |
|--|---------------------|----------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 16 (18.75%) 4 | 2 / 114 (1.75%) 2 |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 15 / 114 (13.16%) 27 |
| Blood and lymphatic system disorders Splenomegaly subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Dental caries subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 2 / 114 (1.75%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 3 / 114 (2.63%) 4 |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Food poisoning subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 1 / 114 (0.88%) 1 |
| Melaena subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|----------------------|
| Nausea subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 4 / 114 (3.51%) 5 |
| Toothache subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 3 / 114 (2.63%) 3 |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Hepatic steatosis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 16 (0.00%) 0 | 0 / 114 (0.00%) 0 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 114 (0.88%) 1 |
| Haemorrhage subcutaneous subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Ingrowing nail subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 114 (0.00%) 0 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 2 | 0 / 16 (0.00%) 0 | 1 / 114 (0.88%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia | | | |

| | | | |
|-----------------------------|-----------------|----------------|-------------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 16 (6.25%) | 9 / 114 (7.89%) |
| occurrences (all) | 1 | 1 | 11 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 16 (0.00%) | 8 / 114 (7.02%) |
| occurrences (all) | 0 | 0 | 10 |
| Extremity contracture | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 1 / 114 (0.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 3 / 114 (2.63%) |
| occurrences (all) | 1 | 0 | 4 |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphangitis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 16 (6.25%) | 0 / 114 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 16 (6.25%) | 22 / 114 (19.30%) |
| occurrences (all) | 3 | 1 | 31 |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| Otitis media | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 1 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 2 / 114 (1.75%) |
| occurrences (all) | 1 | 0 | 2 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 16 (0.00%) | 0 / 114 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 April 2012 | Implemented changes and clarifications secondary to the recommendations of regulatory agencies and in response to specific questions and comments received from pediatric specialists and investigators. The primary revision was a prolongation of the total treatment period from 32 to 36 weeks allowing for a longer observation period after subjects in the prophylaxis treatment arm had been randomized to a less frequent infusion schedule. Stopping rules in the event of inhibitor development were defined and a scheduled data monitoring committee review of the efficacy and safety of BAY94-9027 in the prophylaxis arms was added to occur after approximately 20 subjects had completed 2 months of treatment following randomization. The objectives were modified to clarify that inhibitor development was a specific important safety outcome and an additional laboratory assessment was added to measure possible peak antibody response following the first dose of BAY94-9027. Minor changes included clarification of the time points for PK assessments, the duration of wash-outs required for specific observations, and definition of objective criteria to assess efficacy of surgical interventions. The efficacy variables for Part A were categorized to aid understanding of the outcomes being assessed. |
| 13 December 2012 | Added an optional extension to allow subjects to continue treatment with BAY94-9027 after completion of Part A of the main study. Text was added to more fully define for investigators the effects of the longer half-life of BAY94-9027 on the intervals required for repeat and follow-up infusions for the treatment of bleeds, and additional information for situations when local monitoring of FVIII may have been obtained, including clarification of the reagents that may have been used. Information regarding the available vial sizes, storage, and use of BAY94-9027 was updated. |
| 25 March 2014 | The purpose of the amendment was to add to the protocol an optional extension of Part B to allow subjects to continue to undergo major surgeries using BAY94-9027 during the Part A extension and after ten Part B subjects had completed major surgery. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

"±" in relation with geometric CV is auto-generated. Decimal places automatically truncated. Patient satisfaction & burden were not reported due to concerns regarding instrument development & validation, and translation error in 2 questionnaire items.

Notes: