



Clinical trial results:

A Global, Open-Label, Multicenter, Phase 1/2 Study of the Safety and Dose Escalation of BAX 888, an Adeno-Associated Virus Serotype 8 (AAV8) Vector Expressing B-Domain Deleted Factor VIII (BDD-FVIII) in Severe Hemophilia A Subjects Administered a Single Intravenous Infusion

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005576-22 |
| Trial protocol | IT |
| Global end of trial date | 09 July 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 25 July 2025 |
| First version publication date | 25 July 2025 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 201501 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03370172 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Takeda |
| Sponsor organisation address | 500 Kendall Street, Cambridge, MA, United States, 02142 |
| Public contact | Study Director, Takeda, TrialDisclosures@takeda.com |
| Scientific contact | Study Director, Takeda, TrialDisclosures@takeda.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 July 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 July 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the safety of a single intravenous (IV) infusion of BAX 888 in 2 dose cohorts.

Protection of trial subjects:

Participant signed an informed consent form (ICF) before participating in the study.

Background therapy:

NA

Evidence for comparator:

NA

| | |
|---|------------------|
| Actual start date of recruitment | 27 February 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Spain: 3 |
| Worldwide total number of subjects | 4 |
| EEA total number of subjects | 4 |

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) | 0 |
| Adults (18-64 years) | 4 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 4 participants took part in the study globally from 27 February 2018 to 09 July 2024.

Pre-assignment

Screening details:

Participants with severe Hemophilia A participated in the study to receive BAX 888.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|--|
| Arm title | Cohort 1: BAX 888 2.0×10^{12} cp/kg |
|------------------|--|

Arm description:

Cohort 1 participants received a single peripheral intravenous (IV) infusion of BAX 888 at a dose of 2.0×10^{12} capsid particles per kilogram (cp/kg) on the day of dosing (Day 0).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAX 888 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1 participants received a single peripheral intravenous (IV) infusion of BAX 888 at a dose of 2.0×10^{12} capsid particles per kilogram (cp/kg) on the day of dosing (Day 0).

| | |
|------------------|--|
| Arm title | Cohort 2: BAX 888 6.0×10^{12} cp/kg |
|------------------|--|

Arm description:

Cohort 2 participants received a single peripheral IV infusion of BAX 888 at a dose of 6.0×10^{12} cp/kg on the day of dosing (Day 0).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAX 888 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 2 participants received a single peripheral IV infusion of BAX 888 at a dose of 6.0×10^{12} cp/kg on the day of dosing (Day 0).

| Number of subjects in period 1 | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg |
|---------------------------------------|---|---|
| Started | 2 | 2 |
| Completed | 2 | 1 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: BAX 888 2.0*10 ¹² cp/kg |
|-----------------------|--|

Reporting group description:

Cohort 1 participants received a single peripheral intravenous (IV) infusion of BAX 888 at a dose of 2.0*10¹² capsid particles per kilogram (cp/kg) on the day of dosing (Day 0).

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: BAX 888 6.0*10 ¹² cp/kg |
|-----------------------|--|

Reporting group description:

Cohort 2 participants received a single peripheral IV infusion of BAX 888 at a dose of 6.0*10¹² cp/kg on the day of dosing (Day 0).

| Reporting group values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | Total |
|------------------------|---|---|-------|
| Number of subjects | 2 | 2 | 4 |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---------|--------|---|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 29.5 | 27.5 | |
| standard deviation | ± 13.44 | ± 3.54 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 2 | 2 | 4 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 2 | 2 | 4 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 2 | 2 | 4 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Cohort 1: BAX 888 2.0*10 ¹² cp/kg |
| Reporting group description: Cohort 1 participants received a single peripheral intravenous (IV) infusion of BAX 888 at a dose of 2.0*10 ¹² capsid particles per kilogram (cp/kg) on the day of dosing (Day 0). | |
| Reporting group title | Cohort 2: BAX 888 6.0*10 ¹² cp/kg |
| Reporting group description: Cohort 2 participants received a single peripheral IV infusion of BAX 888 at a dose of 6.0*10 ¹² cp/kg on the day of dosing (Day 0). | |

Primary: Number of Participants With BAX 888-Related Adverse Events (AEs)

| | |
|---|---|
| End point title | Number of Participants With BAX 888-Related Adverse Events (AEs) ^[1] |
| End point description: An AE is defined as any untoward medical occurrence in a participant administered an investigational product (IP) that does not necessarily have a causal relationship with the treatment. A Serious adverse event (SAE) is an AE resulting in any of the following outcomes: death; life-threatening event; required or prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly. AEs include both serious and non-serious adverse events including development of FVIII inhibitory antibodies, clinically significant changes in standard laboratory parameters, physical exam, and vital signs. The Safety Set consisted of all participants who received any amount of investigational product. | |
| End point type | Primary |
| End point timeframe: From first dose up to end of the study (approximately 6 years) | |

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: Only descriptive analyses were planned for this outcome measure.

| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: participants | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Circulating Plasma FVIII Activity Level

| | |
|--|---|
| End point title | Change from Baseline in Circulating Plasma FVIII Activity Level |
| End point description: Change from baseline in circulating plasma FVIII activity level, based on one-stage clotting assay was assessed. The Safety Set consisted of all participants who received any amount of investigational product. Subjects analysed is the number of participants with data available for analysis for this outcome measure. 99999 indicates standard deviation (SD) is not estimable when there is only a single participant. | |

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, up to Month 60 | |

| | | | | |
|---|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 1 | | |
| Units: International Units per deciliter(IU/dL) | | | | |
| arithmetic mean (standard deviation) | 11.40 (± 1.131) | 248.30 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleed Rate (ABR)

| | |
|--|-----------------------------|
| End point title | Annualized Bleed Rate (ABR) |
| End point description: | |
| ABR in comparison to before gene transfer will be assessed. A bleed is defined as subjective or objective evidence of bleeding which may or may not require treatment with FVIII. ABR was calculated as (number of bleeding episodes/observed treatment period in days)*365.25. The Safety Set consisted of all participants who received any amount of investigational product. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 6 years 4 months | |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: bleeds per year | | | | |
| arithmetic mean (standard deviation) | 1.0 (± 1.41) | 0.5 (± 0.71) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Circulating Plasma FVIII Antigen Level

| | |
|-----------------|--|
| End point title | Change from Baseline in Circulating Plasma FVIII Antigen Level |
|-----------------|--|

End point description:

Change from baseline in circulating plasma FVIII antigen (protein) levels were to be assessed. As pre-specified in the statistical analysis plan (SAP), the descriptive analysis for this outcome measure was not performed.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, up to Month 60 | |

| | | | | |
|---|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: international units per milliliter | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[2] - Descriptive analysis for this outcome measure was not performed, as pre-specified in the SAP.

[3] - Descriptive analysis for this outcome measure was not performed, as pre-specified in the SAP.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Reduction in Consumption of Exogenous FVIII

| | |
|-----------------|---|
| End point title | Percentage of Participants With a Reduction in Consumption of Exogenous FVIII |
|-----------------|---|

End point description:

The reduction in consumption of exogenous FVIII was assessed by comparing the amount of exogenous FVIII taken at earliest time point available (prior to BAX 888 infusion) with the amount taken at the last post-infusion timepoint available, during the study. Percentage of participants with reduction in consumption of exogenous FVIII are reported. The Safety Set consisted of all participants who received any amount of investigational product.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 6 years 4 months | |

| | | | | |
|-----------------------------------|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.0 | 0.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Total Binding Antibodies to FVIII

| | |
|--|--|
| End point title | Number of Participants Who Developed Total Binding Antibodies to FVIII |
| End point description: Participants were assessed to check if they developed total binding antibodies to FVIII (Immunoglobulin G [IgG], Immunoglobulin M [IgM]). The Safety Set consisted of all participants who received any amount of investigational product. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 6 years 4 months | |

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Inhibitory Antibodies to FVIII

| | |
|--|---|
| End point title | Number of Participants Who Developed Inhibitory Antibodies to FVIII |
| End point description: Participants were assessed to check if they developed inhibitory antibodies to FVIII. The Safety Set consisted of all participants who received any amount of investigational product. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 6 years 4 months | |

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: participants | 0 | 0 | | |

Statistical analyses

Secondary: Number of Participants With Humoral and Cell-Mediated Immune Response to AAV8 and FVIII Proteins

| | |
|-----------------|--|
| End point title | Number of Participants With Humoral and Cell-Mediated Immune Response to AAV8 and FVIII Proteins |
|-----------------|--|

End point description:

Humoral(antibody-mediated)&cell-mediated immune response to adeno-associated virus(AAV8)(the vector)&FVIII proteins,was assessed.Humoral Immune Response:It is indicated by presence of specific antibodies.Anti-AAV8 binding antibodies,IgG or IgM were measured by enzyme-linked immunosorbent assay(ELISA)method.Neutralizing antibodies were measured by cell-based luminescent assay.Cell-mediated Immune response:AAV8 & FVIII specific cell mediated immunity was assessed using validated interferon- γ (IFN- γ) enzyme-linked immunosorbent spot(ELISpot) assays.This assay tests human T-cell recall response to AAV8 & FVIII proteins.These proteins were called antigens for these tests(AAV8 peptide pools1,2,3&two pooled test antigens(1&2)for FVIII).Number of participants with humoral &/or cell mediated immune response to AAV8 & FVIII proteins,are reported by humoral & cell mediated immune response categories.n:participants with data available for analysis for specified categories.999= 0 subjects analyzed.

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

End point timeframe:

Up to approximately 6 years 4 months

| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: participants | | | | |
| Humoral: Binding Ab to AAV8 IgG Titer (n=2,1) | 2 | 1 | | |
| Humoral: Binding Ab to AAV8 IgM Titer (n=0,0) | 999 | 999 | | |
| Humoral: Neutralising Ab to AAV8 Titer (n=2,1) | 2 | 1 | | |
| Cell-Mediated: AAV8 Peptide Pool 1 Mean (n=2,1) | 0 | 1 | | |
| Cell-Mediated: AAV8 Peptide Pool 2 Mean (n=2,1) | 1 | 1 | | |
| Cell-Mediated: AAV8 Peptide Pool 3 Mean (n=2,1) | 1 | 1 | | |
| Cell-Mediated: FVIII Peptide Pool 1 Mean (n=2,1) | 0 | 0 | | |
| Cell-Mediated: FVIII Peptide Pool 2 Mean (n=2,1) | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Surveillance of AAV8 Genome Shedding

| | |
|-----------------|--------------------------------------|
| End point title | Surveillance of AAV8 Genome Shedding |
|-----------------|--------------------------------------|

End point description:

Surveillance of AAV8 genome shedding in blood, saliva, semen, stool and urine until two consecutive negative results were assessed. 'n' indicates the number of participants with data available for analysis at the specified time points. 99999 indicates SD was not estimable for a single participant. 9999 indicates mean and SD were not estimable due to genome concentrations being Below Limit of Detection and 999 indicates no participant was available for analysis. The Safety Set consisted of all participants who received any amount of investigational product. The data was collected for each category until 2 consecutive measurements are negative.

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

End point timeframe:

Blood: Day 1, weekly at Clinic Visits between Weeks 1-15, and at Months 4 and 5; Saliva, Semen, and Stool: Day 1 and Week 1; Urine: Day 1 and Weeks 1,2,3

| End point values | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: Genome copies per 100 ng of sample | | | | |
| arithmetic mean (standard deviation) | | | | |
| Blood: Day 1 (n=0,1) | 999 (± 999) | 3684434.0 (± 99999) | | |
| Blood: Week 1 (n=1,2) | 3634.0 (± 99999) | 18608.0 (± 664.68) | | |
| Blood: Week 2 (n=2,2) | 2076.0 (± 295.57) | 10670.0 (± 3900.40) | | |
| Blood: Week 3 (n=2,2) | 2069.0 (± 741.05) | 9845.0 (± 6488.41) | | |
| Blood: Week 4 (n=1,2) | 1098.0 (± 99999) | 9033.5 (± 4978.74) | | |
| Blood: Week 5 (n=2,2) | 1483.0 (± 1097.43) | 7884.0 (± 288.50) | | |
| Blood: Week 6 (n=2,2) | 904.0 (± 335.17) | 5372.5 (± 441.94) | | |
| Blood: Week 7 (n=2,2) | 1004.0 (± 656.20) | 6808.0 (± 1121.47) | | |
| Blood: Week 8 (n=2,2) | 828.5 (± 267.99) | 7384.0 (± 1011.16) | | |
| Blood: Week 9 (n=2,2) | 714.5 (± 222.74) | 6384.5 (± 195.87) | | |
| Blood: Week 10 (n=2,2) | 773.0 (± 9.90) | 6144.5 (± 939.74) | | |
| Blood: Week 11 (n=2,2) | 755.0 (± 241.83) | 3935.0 (± 1547.15) | | |
| Blood: Week 12 (n=2,2) | 728.0 (± 130.11) | 3893.5 (± 276.48) | | |
| Blood: Week 13 (n=2,2) | 654.0 (± 22.63) | 3044.5 (± 1191.47) | | |
| Blood: Week 14 (n=2,2) | 735.5 (± 82.73) | 2856.0 (± 1473.61) | | |
| Blood: Week 15 (n=1,2) | 742.0 (± 99999) | 2812.0 (± 2083.14) | | |
| Blood: Month 4 (n=2,1) | 422.0 (± 192.33) | 3066.0 (± 99999) | | |
| Blood: Month 5 (n=0,1) | 999 (± 999) | 210.0 (± 99999) | | |

| | | | | |
|------------------------|------------------|--------------------|--|--|
| Saliva: Day 1 (n=2,2) | 935.0 (± 268.70) | 2076.5 (± 473.05) | | |
| Saliva: Week 1 (n=0,2) | 999 (± 999) | 352.5 (± 12.02) | | |
| Semen: Day 1 (n=1,2) | 55.0 (± 99999) | 230.5 (± 188.80) | | |
| Semen: Week 1 (n=0,1) | 999 (± 999) | 194.0 (± 99999) | | |
| Stool: Day 1 (n=0,1) | 999 (± 999) | 5985.0 (± 99999) | | |
| Stool: Week 1 (n=0,2) | 999 (± 999) | 7164.0 (± 7993.14) | | |
| Urine: Day 1 (n=2,2) | 9999 (± 9999) | 9999 (± 9999) | | |
| Urine: Week 1 (n=2,2) | 9999 (± 9999) | 9999 (± 9999) | | |
| Urine: Week 2 (n=2,2) | 9999 (± 9999) | 9999 (± 9999) | | |
| Urine: Week 3 (n=2,2) | 9999 (± 9999) | 9999 (± 9999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to approximately 6 years 4 months; SAEs and Other (Non-Serious) AEs: From first dose up to end of the study (approximately 6 years)

Adverse event reporting additional description:

The Safety Set consisted of all participants who received any amount of investigational product.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: BAX 888 6.0*10 ¹² cp/kg |
|-----------------------|--|

Reporting group description:

Cohort 2 participants received a single peripheral IV infusion of BAX 888 at a dose of 6.0*10¹² cp/kg on the day of dosing (Day 0).

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: BAX 888 2.0*10 ¹² cp/kg |
|-----------------------|--|

Reporting group description:

Cohort 1 participants received a single peripheral intravenous (IV) infusion of BAX 888 at a dose of 2.0*10¹² capsid particles per kilogram (cp/kg) on the day of dosing (Day 0).

| Serious adverse events | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort 2: BAX 888 6.0*10 ¹² cp/kg | Cohort 1: BAX 888 2.0*10 ¹² cp/kg | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 2 (100.00%) | |
| Vascular disorders | | | |

| | | | |
|---|--|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 | |
| General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 2 0 / 2 (0.00%) 0 | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 | |
| Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 | |
| Investigations SARS-CoV-2 test positive subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 | 2 / 2 (100.00%) 2 0 / 2 (0.00%) 0 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Ligament sprain | 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 | |
| Nervous system disorders Migraine subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 3 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 1 / 2 (50.00%) 1 1 / 2 (50.00%) 6 | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 1 / 2 (50.00%) 2 | |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 2 (0.00%) 0 | |
| Gastrointestinal disorders Tongue geographic subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 1 / 2 (50.00%) 2 | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 | |
| Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all) | 2 / 2 (100.00%) 2 | 2 / 2 (100.00%) 3 | |

| | | | |
|---|----------------|----------------|--|
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatosis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Synovitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Arthritis | | | |

| | | | |
|------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 2 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 1 | 1 | |
| Tendon disorder | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 2 / 2 (100.00%) | |
| occurrences (all) | 0 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 1 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hyperphagia | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Hypophosphataemia | | | |

| | | | |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Increased appetite | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 15 March 2017 | The following changes were made as per Amendment 1: 1. Updated timelines and added an extension trial timeline. 2. Increased target improvement in FVIII from 5% to 20%. 3. Expanded the description of the benefits and the risks. 4. Increased target proportion of participants with improvement in FVII from 50% to 60%. 5. Simplified the original 3 cohort, parallel group design to allow 2 cohorts in sequence. |
| 24 January 2018 | The following changes were made as per Amendment 4: 1. Added Months 24 and 36 to Hemophilia Joint Health Score assessment. 2. Added collection of untoward events in e-diary. 3. Extended exclusion criterion relating to known hypersensitivity to prednisolone or prednisone to also include hypersensitivity to any of the excipients. |
| 16 August 2018 | The following changes were made as per Amendment 5: 1. Eliminated Exclusion Criterion 5: "Positive AAV8 specific T-cell ELISPOTs for any AAV8 peptide pools" and deletion of optional assessment: CMI response to AAV8 and FVIII transgene products (if Screening 2 was longer than 4 weeks from Screening 1). 2. Deleted nonclinical Dose Response Study and Toxicity Study, and added reference to investigator's Brochure. 3. Deleted administration of 10% of the BAX 888 with "a syringe driver pump" to maintain consistency with BAX 888 Study Pharmacy Manual. 4. Added language to allow additional analyses on efficacy and safety data at trial milestones. |
| 03 May 2019 | The following changes were made as per Amendment 6: 1. Added Cohort 3. 2. Deleted dose escalation triggered by Week 4 FVIII activity levels from Cohort 2. 3. Updated recruitment period. 4. Updated targeted accrual to reflect addition of Cohort 3. 5. Deleted the Short (Accelerated) Tapering Regimen for corticosteroids. 6. Updated immunosuppression with prophylactic corticosteroids. |
| 12 March 2020 | The following changes were made as per Amendment 7: 1. Specified the minimum data on which the DMC recommendation will be based. 2. Updated cohort expansion rules for Cohort 2. 3. Updated cohort expansion and rules for dose escalation to Cohort 2 and Cohort 3 doses. 4. Lowered the dose for Cohort 3 from 1.8×10^{13} cp/kg to 1.2×10^{13} cp/kg. 5. Deleted Inclusion Criterion 4 (normal prothrombin time) and instead inserted new Exclusion Criterion 17 to provide upper limit of prothrombin time international normalized ratio. 6. Added AAV2 binding and neutralizing antibodies as exploratory assay. |
| 22 March 2021 | The following changes were made as per Amendment 8: 1. Revised Trial Completion Date to Q3 2026. 2. Revised trial duration from 5 years to 8 years. 3. Deleted text regarding an additional 2 years in an extension trial. 4. Added evaluations at Months 36, 48, and 60. 5. Added long-term safety and efficacy evaluations annually at years 4 and 5. 6. Increased overall duration of the trial from 6 to 8 years because trial completion was changed from 3 to 5 years post gene transfer. |
| 10 November 2021 | The following changes were made as per Amendment 9: 1. Updated sponsor information and protocol history on the Title Page, Protocol signature page, Section 14.6, Figure 2, and Figure 3. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported