Clinical trial results:
A Post Approval Commitment study to evaluate the efficacy, safety, and pharmacokinetics of KOVALTRY in Chinese children, adolescents/adults with severe hemophilia A.

Summary

EudraCT number	2021-003537-11
Trial protocol	Outside EU/EEA
Global end of trial date	15 March 2024

Results information

Result version number	v1 (current)
This version publication date	22 September 2024
First version publication date	22 September 2024

Trial information

Trial identification

Sponsor protocol code	BAY81-8973/19855

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04565236
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To evaluate the efficacy of prophylaxis treatment with KOVALTRY in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe hemophilia A.
Part B: To assess the efficacy of KOVALTRY within 48 hours of previous prophylaxis infusion in previously untreated/minimally treated Chinese children (<6 years of age) with severe hemophilia A.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects (or their legally authorized representative according to local legislation). Participating subjects (or their legally authorized representative according to local legislation) 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	22 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 45
Worldwide total number of subjects	45
EEA total number of subjects	0

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)	1
Children (2-11 years)	32

Adolescents (12-17 years)	5
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Part A of study was conducted in multicenter in China between 22 SEP 2020 and 04 JAN 2022. The Part B of study was conducted in multicenter in China between 07 SEP 2021 and 15 MAR 2024.

Pre-assignment

Screening details:

A total of 44 subjects were enrolled in Part A of the study. Of these, 2 subjects did not pass screening and 42 subjects participated in Part A. A total of 3 participants were enrolled in Part B of the study, and all of them passed screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: PTPs <12 years

Arm description:

Previously treated severe hemophilia A patients (PTPs) aged below 12 years received KOVALTRY prophylaxis and treatment.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII (KOVALTRY, BAY81-8973)
Investigational medicinal product code	BAY81-8973
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 to 50 IU of KOVALTRY per kg body weight (rounded to the nearest vial size) twice weekly, three times weekly, or every other day according to individual requirements

Arm title	Part A: PTPs ≥12 years

Arm description:

Previously treated severe hemophilia A patients (PTPs) aged 12 to 65 years received KOVALTRY for prophylaxis and treatment.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII (KOVALTRY, BAY81-8973)
Investigational medicinal product code	BAY81-8973
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 years: 25 to 50 IU of KOVALTRY per kg body weight (rounded to the nearest vial size) twice weekly, three times weekly, or every other day according to individual requirements;
>12 years: 20 to 40 IU of KOVALTRY per kg of body weight (rounded to the nearest vial size) two or three times per week according to individual requirements

Arm title	Part B: PUPs <6 years

Arm description:

Previously untreated severe hemophilia A patients (PUPs) aged below 6 years of age received KOVALTRY for prophylaxis and treatment.

Arm type	Experimental

Investigational medicinal product name	Recombinant Factor VIII (KOVALTRY, BAY81-8973)
Investigational medicinal product code	BAY81-8973
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 to 50 IU (minimum 250 IU) of KOVALTRY per kg body weight (rounded to the nearest vial size) at least 1 day per week.
Alternatively, prophylaxis could be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight.

Arm title	Part B: MTPs <6 years

Arm description:

Minimally treated severe hemophilia A patients (MTPs) aged below 6 years received KOVALTRY for prophylaxis and treatment.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII (KOVALTRY, BAY81-8973)
Investigational medicinal product code	BAY81-8973
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 to 50 IU (minimum 250 IU) of KOVALTRY per kg body weight (rounded to the nearest vial size) at least 1 day per week. Alternatively, prophylaxis could be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight.

Number of subjects in period 1	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years
Started	30	12	2
Completed	30	12	1
Not completed	0	0	1
Patient/Guardian Decision	-	-	1

Number of subjects in period 1	Part B: MTPs <6 years
Started	1
Completed	1
Not completed	0
Patient/Guardian Decision	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: PTPs <12 years
Reporting group description:	
Previously treated severe hemophilia A patients (PTPs) aged below 12 years received KOVALTRY prophylaxis and treatment.	
Reporting group title	Part A: PTPs ≥12 years
Reporting group description:	
Previously treated severe hemophilia A patients (PTPs) aged 12 to 65 years received KOVALTRY for prophylaxis and treatment.	
Reporting group title	Part B: PUPs <6 years
Reporting group description:	
Previously untreated severe hemophilia A patients (PUPs) aged below 6 years of age received KOVALTRY for prophylaxis and treatment.	
Reporting group title	Part B: MTPs <6 years
Reporting group description:	
Minimally treated severe hemophilia A patients (MTPs) aged below 6 years received KOVALTRY for prophylaxis and treatment.	

Reporting group values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years
Number of subjects	30	12	2
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	1
Children (2-11 years)	30	0	1
Adolescents (12-17 years)	0	5	0
Adults (18-64 years)	0	7	0
Sex: Female, Male Units: participants			
Female	0	0	0
Male	30	12	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	30	12	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Part B: MTPs <6 years	Total	
Number of subjects	1	45	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	1	

Children (2-11 years)	1	32	
Adolescents (12-17 years)	0	5	
Adults (18-64 years)	0	7	
Sex: Female, Male Units: participants			
Female	0	0	
Male	1	45	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	45	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Part A: PTPs <12 years
Reporting group description:	
Previously treated severe hemophilia A patients (PTPs) aged below 12 years received KOVALTRY prophylaxis and treatment.	
Reporting group title	Part A: PTPs ≥12 years
Reporting group description:	
Previously treated severe hemophilia A patients (PTPs) aged 12 to 65 years received KOVALTRY for prophylaxis and treatment.	
Reporting group title	Part B: PUPs <6 years
Reporting group description:	
Previously untreated severe hemophilia A patients (PUPs) aged below 6 years of age received KOVALTRY for prophylaxis and treatment.	
Reporting group title	Part B: MTPs <6 years
Reporting group description:	
Minimally treated severe hemophilia A patients (MTPs) aged below 6 years received KOVALTRY for prophylaxis and treatment.	
Subject analysis set title	Modified Intent-To-Treat (mITT) population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All study subjects who had infusion/bleeding data from the electronic patient diary (EPD) and/or case report form (CRF).	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects enrolled into the study and received at least 1 dose of study drug.	
Subject analysis set title	Pharmacokinetic analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects with evaluable PK data	

Primary: Annualized bleeding rate (ABR) of all bleeding episodes during prophylaxis treatment in Part A

End point title	Annualized bleeding rate (ABR) of all bleeding episodes during prophylaxis treatment in Part A[1][2]
End point description:	
Annualized number (mean +/- standard deviation) of all bleeding episodes that occurred during the prophylaxis treatment period is reported for previously treated patients (PTPs). All bleeding episodes: sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery.	
End point type	Primary
End point timeframe:	
Up to 6 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "ABR of all bleeding episodes during prophylaxis treatment in Part B" is reported as a separate endpoint.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[3]	12[4]		
Units: Bleed per year				
arithmetic mean (standard deviation)	3.38 (± 4.17)	1.86 (± 2.54)		

Notes:

[3] - mITT

[4] - mITT

Statistical analyses

No statistical analyses for this end point

Primary: Annualized bleeding rate (ABR) of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part B

End point title	Annualized bleeding rate (ABR) of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part B[5][6]

End point description:

Annualized number (mean +/- standard deviation) of all bleeding episodes that occurred within 48 hours of previous prophylaxis infusion is reported for previously untreated/minimally treated patients (PUPs/MTPs). All bleeding episodes: sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery.

End point type	Primary

End point timeframe:

Up to 48 hours post-infusion during 6 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.
[6] - 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: "ABR of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part A" is reported as a separate endpoint.

End point values	Part B: PUPs <6 years	Part B: MTPs <6 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[7]	1[8]		
Units: Bleed per year				
arithmetic mean (standard deviation)	0.00 (± 0.00)	0.00 (± 0.00)		

Notes:

[7] - mITT

[8] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate (ABR) of all bleeding episodes during prophylaxis treatment in Part B

End point title	Annualized bleeding rate (ABR) of all bleeding episodes during prophylaxis treatment in Part B[9]

End point description:

Annualized number (mean +/- standard deviation) of all bleeding episodes that occurred during the

prophylaxis treatment period is reported for previously untreated/minimally treated patients (PUPs/MTPs). All bleeding episodes: sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery.

End point type	Secondary

End point timeframe:

Up to 51 exposure days

Notes:

[9] - 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: "ABR of all bleeding episodes during prophylaxis treatment in Part A" is reported as a separate endpoint.

End point values	Part B: PUPs <6 years	Part B: MTPs <6 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[10]	1[11]		
Units: Bleed per year				
arithmetic mean (standard deviation)	1.13 (± 1.60)	2.05 (± 0)		

Notes:

[10] - mITT

[11] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate (ABR) of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part A

End point title	Annualized bleeding rate (ABR) of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part A[12]

End point description:

Annualized number (mean +/- standard deviation) of all bleeding episodes that occurred within 48 hours of previous prophylaxis infusion is reported for previously treated patients (PTPs). All bleeding episodes: sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery.

End point type	Secondary

End point timeframe:

Up to 48 hours post-infusion during 6 months

Notes:

[12] - 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: "ABR of all bleeding episodes within 48 hours of previous prophylaxis infusion in Part B" is reported as a separate endpoint.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[13]	12[14]		
Units: Bleed per year				
arithmetic mean (standard deviation)	2.26 (± 3.10)	1.36 (± 2.19)		

Notes:

[13] - mITT

[14] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions per bleeding episode

End point title	Number of infusions per bleeding episode

End point description:

The mean value of number of infusions for the treatment of one bleed to achieve hemostasis is reported.

End point type	Secondary

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17[15]	5[16]	1[17]	1[18]
Units: Infusion				
arithmetic mean (standard deviation)	1.78 (± 2.28)	1.45 (± 1.29)	14.00 (± 0.00)	1.00 (± 0.00)

Notes:

[15] - Subjects in mITT with any bleed

[16] - Subjects in mITT with any bleed

[17] - Subjects in mITT with any bleed

[18] - Subjects in mITT with any bleed

Statistical analyses

No statistical analyses for this end point

Secondary: FVIII in-vivo recovery in Part A

End point title	FVIII in-vivo recovery in Part A[19]

End point description:

Incremental recovery of Factor VIII (FVIII) was determined by collecting blood samples pre-infusion and 15-30 minutes after the end of the infusion. Mean recovery values at different time points are reported.

End point type	Secondary

End point timeframe:

At baseline, Month 2 and final visit

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "FVIII in-vivo recovery in Part B" is reported as a separate endpoint.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[20]	12[21]		
Units: IU/dL per IU/kg				
arithmetic mean (standard deviation)				
Baseline	1.82 (± 0.26)	2.03 (± 0.46)		
Month 2	1.86 (± 0.32)	2.12 (± 0.42)		
Final visit	1.85 (± 0.33)	2.06 (± 0.37)		

Notes:

[20] - mITT, n=28 at baseline, =30 at Month 2 and final visit

[21] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeds per physician’s assessment of adequacy of hemostasis in minor surgery

End point title	Number of bleeds per physician’s assessment of adequacy of hemostasis in minor surgery

End point description:

For subjects who underwent minor surgeries during the study, investigators were ask to assess the adequacy of hemostasis during the surgeries as excellent, good, moderate or poor. Number of surgeries per assessment is reported.

End point type	Secondary

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[22]	1[23]	0[24]	0[25]
Units: Surgery				
number (not applicable)				
Total minor surgeries	2	2		
Surgeries with EXCELLENT adequacy of hemostasis	2	2		

Notes:

[22] - Subjects in mITT with minor surgeries

[23] - Subject in mITT with minor surgeries

[24] - No subject with minor surgery

[25] - No subject with minor surgery

Statistical analyses

No statistical analyses for this end point

Secondary: FVIII in-vivo recovery in Part B

End point title	FVIII in-vivo recovery in Part B[26]

End point description:

Incremental recovery of Factor VIII (FVIII) was determined by collecting blood samples pre-infusion and 15-30 minutes after the end of the infusion. Mean recovery values at different time points are reported. "99999" denotes that value could not be calculated because value of FVIII was not measured or because of missing values.

End point type	Secondary

End point timeframe:

At baseline, Visit 6 (ED 20), unscheduled visit and final visit

Notes:

[26] - 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: "FVIII in-vivo recovery in Part A" is reported as a separate endpoint.

End point values	Part B: PUPs <6 years	Part B: MTPs <6 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[27]	1[28]		
Units: IU/dL per IU/kg				
arithmetic mean (standard deviation)				
Baseline (Unscheduled visit for PUP)	1.90 (± 0.00)	1.86 (± 0.00)		
Visit 6 (ED 20)	0.91 (± 0.00)	1.22 (± 0.00)		
Final visit	1.55 (± 0.00)	99999 (± 99999)		

Notes:

[27] - Subject in mITT with calculable recovery value at any time points

[28] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Factor VIII inhibitor development by the Nijmegen Bethesda assay

End point title	Factor VIII inhibitor development by the Nijmegen Bethesda assay

End point description:

Number of subjects who developed a positive Factor VIII (FVIII) inhibitor level (≥0.6 Bethesda unit [BU/mL]) during the study is reported.

End point type	Secondary

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[29]	12[30]	2[31]	1[32]
Units: Subject	0	0	0	0

Notes:

[29] - SAF

[30] - SAF

[31] - SAF

[32] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment-emergent adverse events

End point title	Number of participants with treatment-emergent adverse events

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject, associated with the use of study intervention, whether or not considered related to the study intervention. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening; persistent or significant disability/incapacity; congenital anomaly/birth defect; another medical important serious event as judged by the investigator. AEs or SAEs were considered to be treatment emergent (TEAEs or TESAEs) if they started after the first KOVALTRY infusion and up to 3 days after the last dose.

End point type	Secondary

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[33]	12[34]	2[35]	1[36]
Units: Subject				
Any TEAE	13	3	1	1
Maximum intensity for any TEAE - Mild	10	3	1	1
Maximum intensity for any TEAE - Moderate	2	0	0	0
Maximum intensity for any TEAE - Severe	1	0	0	0
Any study drug-related TEAE	1	0	0	0
Any TESAE	2	0	0	0
TEAE with outcome death	0	0	0	0

Notes:

[33] - SAF

[34] - SAF

[35] - SAF

[36] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration of FVIII in plasma (Cmax) in Part A

End point title	Maximum observed concentration of FVIII in plasma (Cmax) in Part A[37]

End point description:

For the assessment, subjects were administered a dose of 50 IU/kg KOVALTRY. Subjects must have no signs or symptoms of an acute bleeding episode. For subjects below 12 years, the evaluation was only performed once at baseline. For adolescents/adult participants 12 years or older, the evaluation was performed twice at baseline and at final visit. "99999" denotes that value was not calculated as no evaluation was performed.

End point type	Secondary

End point timeframe:

Pre-infusion and up to 30 minutes post-infusion

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analysis was only planned for Part A.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[38]	12[39]		
Units: IU/dL				
geometric mean (geometric coefficient of variation)				
Baseline	95.20 (± 15.24)	114.64 (± 15.77)		
Final Visit/ Early Termination	99999 (± 99999)	115.95 (± 17.47)		

Notes:

[38] - PKS

[39] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration of FVIII versus time curve from zero to infinity (AUC) in Part A

End point title	Area under the plasma concentration of FVIII versus time curve from zero to infinity (AUC) in Part A[40]

End point description:

For the assessment, subjects were administered a dose of 50 IU/kg KOVALTRY. Subjects must have no signs or symptoms of an acute bleeding episode. For subjects below 12 years, the evaluation was only performed once at baseline. For adolescents/adult participants 12 years or older, the evaluation was performed twice at baseline and at final visit. "99999" denotes that value was not calculated as no evaluation was performed.

End point type	Secondary

End point timeframe:

Pre-infusion and up to 24 hours post-infusion in subjects < 12 years or up to 48 hours post-infusion in subjects ≥ 12 years

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analysis was only planned for Part A.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[41]	12[42]		
Units: h*IU/dL				
geometric mean (geometric coefficient of variation)				
Baseline	1292.97 (± 22.87)	1519.38 (± 32.38)		
Final Visit/ Early Termination	99999 (± 99999)	1559.29 (± 26.16)		

Notes:

[41] - PKS

[42] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of FVIII in plasma in Part A

End point title	Half-life (t1/2) of FVIII in plasma in Part A[43]

End point description:

For the assessment, subjects were administered a dose of 50 IU/kg KOVALTRY. Subjects must have no signs or symptoms of an acute bleeding episode. For subjects below 12 years, the evaluation was only performed once at baseline. For adolescents/adult participants 12 years or older, the evaluation was performed twice at baseline and at final visit.

End point type	Secondary

End point timeframe:

Pre-infusion and up to 24 hours post-infusion in subjects < 12 years or up to 48 hours post-infusion in subjects ≥ 12 years

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analysis was only planned for Part A.

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[44]	12[45]		
Units: Hour				
geometric mean (geometric coefficient of variation)				
Baseline	10.3655 (± 21.22)	11.8605 (± 19.25)		
Final Visit/ Early Termination	99999 (± 99999)	11.2630 (± 17.29)		

Notes:

[44] - PKS

[45] - PKS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects without bleeding episode

End point title	Number of subjects without bleeding episode

End point description:

Number of subjects who did not experience any bleed during the prophylaxis treatment period or within 48 hours of previous prophylaxis infusion is reported.

End point type	Other pre-specified

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[46]	12[47]	2[48]	1[49]
Units: Subject				
During prophylaxis treatment	13	7	1	0
Within 48 hours	16	8	2	1

Notes:

[46] - mITT

[47] - mITT

[48] - mITT

[49] - mITT

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of bleeds per assessment of response to treatment of bleeds

End point title	Number of bleeds per assessment of response to treatment of bleeds

End point description:

Subjects or caregivers were asked to assess the response to treatment of bleeds as excellent, good, moderate or poor. Number of bleeds per assessment is reported.

End point type	Other pre-specified

End point timeframe:

Part A: up to 6 months; Part B: up to 51 exposure days

End point values	Part A: PTPs <12 years	Part A: PTPs ≥12 years	Part B: PUPs <6 years	Part B: MTPs <6 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30[50]	12[51]	2[52]	1[53]
Units: Bleed				
Total bleeds	51	11	1	1
Bleeds without response assessment to treatment	7	1	0	0
Bleeds with EXCELLENT response to treatment	4	5	0	0
Bleeds with GOOD response to treatment	25	2	0	1
Bleeds with MODERATE response to treatment	14	3	1	0
Bleeds with POOR response to treatment	1	0	0	0

Notes:

[50] - mITT

[51] - mITT

[52] - mITT

[53] - mITT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first infusion and not later than three days after the last infusion in Part A or Part B. Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Part A: PTPs <12 years

Reporting group description:

Previously treated severe hemophilia A patients (PTPs) aged below 12 years received KOVALTRY prophylaxis and treatment

Reporting group title	Part A: PTPs >=12 years

Reporting group description:

Previously treated severe hemophilia A patients (PTPs) aged 12 to 65 years received KOVALTRY for prophylaxis and treatment

Reporting group title	Part B: PUPs <6 years

Reporting group description:

Previously untreated severe hemophilia A patients (PUPs) aged below 6 years of age received KOVALTRY for prophylaxis

Reporting group title	Part B: MTPs <6 years

Reporting group description:

Minimally treated severe hemophilia A patients (MTPs) aged below 6 years received KOVALTRY for prophylaxis

Serious adverse events	Part A: PTPs <12 years	Part A: PTPs >=12 years	Part B: PUPs <6 years
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	0 / 12 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 12 (0.00%)	0 / 2 (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
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 30 (3.33%)	0 / 12 (0.00%)	0 / 2 (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

Serious adverse events	Part B: MTPs <6 years		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A: PTPs <12 years	Part A: PTPs >=12 years	Part B: PUPs <6 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)	3 / 12 (25.00%)	1 / 2 (50.00%)
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 30 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Duodenal ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 12 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Infections and infestations			
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 30 (13.33%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0
Upper respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 30 (16.67%)	1 / 12 (8.33%)	0 / 2 (0.00%)
occurrences (all)	10	1	0
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
COVID-19			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 12 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: MTPs <6 years		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders Hypertension alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Gastrointestinal disorders Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Duodenal ulcer alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all) Rhinorrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Infections and infestations Tonsillitis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Upper respiratory tract infection alternative assessment type: Systematic subjects affected / exposed occurrences (all) Respiratory tract infection alternative assessment type: Systematic	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 		

subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
COVID-19			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2020	Amendment 1 specified the following modifications: - Addition of previously untreated patients (PUPs) and minimally treated patients (MTPs) to the study such that the study had 2 parts (Part A for previously treated patients and Part B for PUPs/MTPs) to fulfill post approval commitment received from the China Center for Drug Evaluation (CDE) and China National Medical Products Administration (NMPA). - Addition of a new section to describe optional immune tolerance induction (ITI) therapy to provide management options to participants who developed high titer FVIII inhibitor. - Change in the CRF location of documentation of AEs from Medical History section to AE Report Form to correct reporting process for AEs.
12 May 2023	Amendment 2 specified the following modifications, but no subject had been enrolled under this protocol amendment: - Changed all the assays planned in central lab to local lab for Part B. - Removed the Combined Screening and Baseline (PUPs only) in Part B. - Removed FVIII trough level assessment from Visit 2 in Part B. - The chromogenic assay was changed to one-stage clotting assay in all plasma concentrations of FVIII measurement for Part B.

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.

Occurrence of "±" in relation with coefficient of variation is auto-generated by the database. Results of ABR of treated/target joint bleeding episodes and FVIII usage are not reported as they are other pre-defined endpoints per protocol.

Notes: