Clinical trial results:
Post-marketing investigation (PMI) to assess safety and efficacy of Jivi (BAY 94-9027) treatment in patients with hemophilia A

Summary

EudraCT number	2018-003655-37
Trial protocol	NO DK ES PL BG GR IT
Global end of trial date	26 August 2022

Results information

Result version number	v1 (current)
This version publication date	11 August 2023
First version publication date	11 August 2023

Trial information

Trial identification

Sponsor protocol code	19764

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04085458
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety of Jivi

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. Participating subjects 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 September 2019
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	Bulgaria: 3
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 4
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	32
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 13 centers in 7 countries between 23 SEP 2019 (First subject first visit) and 26 Aug 2022 (last subject's data from the last visit were received). Bulgaria (2 centers), Denmark (1 centers), Spain (3 centers), Greece (1 center), Italy (3 centers), Norway (1 center), Poland (2 centers).

Pre-assignment

Screening details:

36 subjects were screened into the study (signed informed consent form (ICF)). 4 subjects were screening failed.

Period 1

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

Arms

Arm title	Severe hemophilia A patients with Jivi treatment

Arm description:

Prophylaxis regimens with every 5 days treatment (45-60 IU/kg), or every 7 days (60 IU/kg) or twice per week (40 IU/kg).

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol (Jivi, BAY94-9027)
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosage regimens were every 5 days treatment (45-60 IU/kg), or every 7 days (60 IU/kg) or twice per week (40 IU/kg).

Number of subjects in period 1[1]	Severe hemophilia A patients with Jivi treatment
Started	32
Completed	27
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Other	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Number of subjects worldwide (36) were subjects who signed informed consent form (ICF)). Number of subjects in baseline (32) were subjects who received study intervention.

Baseline characteristics

Reporting groups	
Reporting group title	Severe hemophilia A patients with Jivi treatment
Reporting group description:	
Prophylaxis regimens with every 5 days treatment (45-60 IU/kg), or every 7 days (60 IU/kg) or twice per week (40 IU/kg).	

Reporting group values	Severe hemophilia A patients with Jivi treatment	Total	
Number of subjects	32	32	
Age Categorical Units: Subjects			
Adults (18-64 years)	29	29	
From 65-84 years	3	3	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42.8		
standard deviation	± 15.1	-	
Gender Categorical Units: subjects			
Female	0	0	
Male	32	32	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	32	32	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	30	30	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Severe hemophilia A patients with Jivi treatment
Reporting group description:	
Prophylaxis regimens with every 5 days treatment (45-60 IU/kg), or every 7 days (60 IU/kg) or twice per week (40 IU/kg).	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
A subject was included in the SAF if he received at least 1 infusion of study drug.	
Subject analysis set title	Modified intent-to-treat set (mITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A subject was included in the mITT if he received at least 1 infusion of study drug and had injection/bleeding data available for at least 3 months. This time period is considered the minimum observation time for a reliable annualization of the observed bleed rate.	

Primary: FVIII inhibitor development by the Nijmegen Bethesda assay

End point title	FVIII inhibitor development by the Nijmegen Bethesda assay[1]
End point description:	
FVIII inhibitor testing was performed using the Nijmegen-modified Bethesda assay. A positive inhibitor result was defined as a threshold of ≥0.6 BU/mL at the central laboratory and had to be confirmed with a second blood sample. After confirmation of the positive result, the inhibitor was to be reported as an SAE. The analysis of this end point was performed on the SAF.	
End point type	Primary
End point timeframe:	
Observed for 100 exposure days (EDs), up to 2 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: There were no subjects with a positive FVIII inhibitor measurement, therefore, there was no statistical analysis

End point values	Severe hemophilia A patients with Jivi treatment			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: subjects				
number (not applicable)				
Any positive FVIII inhibitor	0			
High titer FVIII inhibitor	0			
Low titer FVIII inhibitor	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events

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

End point description:

Treatment-emergent AEs were defined as those that started after the first dose of study drug and up to 7 days after the last dose. The analysis of this end point was performed on the SAF.

End point type	Secondary

End point timeframe:

Observed for 100 exposure days (EDs), up to 2 years.

End point values	Severe hemophilia A patients with Jivi treatment			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: subjects				
Any AE	21			
Any study drug-related AE	3			
Any AE related to protocol required procedures	0			
Any AE leading to discontinuation of study drug	2			
Any SAE	2			
Any study drug-related SAE	0			
Any SAE related to protocol required procedures	0			
Any SAE leading to discontinuation of study drug	0			
AE with outcome death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of treatment-emergent anti-PEG antibodies

End point title	Development of treatment-emergent anti-PEG antibodies

End point description:

Anti-PEG antibody: antibody against the PEG moiety determined by enzyme-linked immunosorbent assay (ELISA). For participants with a positive result, IgM antibodies were tested.

End point type	Secondary

End point timeframe:

Observed for 100 exposure days (EDs), up to 2 years.

End point values	Severe hemophilia A patients with Jivi treatment			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: subjects				
Low titer PEG antibody (transient)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate (ABR)

End point title	Annualized bleeding rate (ABR)

End point description:

ABR is number of all bleeds per individual treatment period annualized to a 1-year time interval. The analysis of this end point was performed on the mITT.

End point type	Secondary

End point timeframe:

Observed for 100 exposure days (EDs), up to 2 years.

End point values	Severe hemophilia A patients with Jivi treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Bleeds per year				
median (inter-quartile range (Q1-Q3))	1.8 (0.7 to 5.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for TEAEs: After the first study intervention up to 7 days after the end of study intervention with an average of 475 days. Timeframe for deaths (all causes): with an average of 476 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	BAY94-9027 prophylaxis treatment

Reporting group description:

The recommended starting dose was every 5 days treatment (45 IU/kg). An assessment of response to treatment will be performed at the next scheduled visit after 10-15 ED (8-10 weeks). Thereafter, participants may be assigned to different dosing regimens (every 7 days or 2x/week) or continue with every 5 days regimen, according to individual bleeding tendency and needs at investigator's discretion.

Serious adverse events	BAY94-9027 prophylaxis treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BAY94-9027 prophylaxis treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 32 (46.88%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2020	Amendment 1 was prepared to incorporate Health Authority feedback regarding the definitions for the end of study and adverse events, assessment of body weight at additional visits, and clarification that screen failures may be re-screened once.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported