Clinical trial results:
Multiple escalating dose study of BAY 1093884 in adults with hemophilia A or B with or without inhibitors

Summary

EudraCT number	2017-003324-67
Trial protocol	GB AT BG FR HU IT
Global end of trial date	15 October 2019

Results information

Result version number	v1 (current)
This version publication date	28 October 2020
First version publication date	28 October 2020

Trial information

Trial identification

Sponsor protocol code	BAY1093884/19580

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03597022
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	15 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of multiple subcutaneous doses of befovacimab in subjects with hemophilia A or B with or without inhibitors

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	24 July 2018
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	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	24
EEA total number of subjects	16

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)	23
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 11 countries or regions between 24 July 2018 (first subject first visit) and 15 October 2019 (last subject last visit).

Pre-assignment

Screening details:

Overall, 26 subjects were screened. Of them, 1 subject was screen failure and 1 subject could not start subsequent treatment on schedule; 24 subjects received study treatment.

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?	Yes
Arm title	BAY1093884 100mg

Arm description:

Subjects received BAY1093884 100 mg once a week until premature termination of the study

Arm type	Experimental
Investigational medicinal product name	Befovacimab
Investigational medicinal product code	BAY1093884
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100 mg, once weekly doses until premature termination of the study, subcutaneous injection

Arm title	BAY1093884 225mg

Arm description:

Subjects received BAY1093884 225 mg once a week until premature termination of the study

Arm type	Experimental
Investigational medicinal product name	Befovacimab
Investigational medicinal product code	BAY1093884
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

225 mg, once weekly doses until premature termination of the study, subcutaneous injection

Arm title	BAY1093884 400mg

Arm description:

Subjects received BAY1093884 400mg once a week until premature termination of the study

Arm type	Experimental
Investigational medicinal product name	Befovacimab
Investigational medicinal product code	BAY1093884
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
400 mg, once weekly doses until premature termination of the study, subcutaneous injection

Number of subjects in period 1	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg
Started	8	8	8
Completed	0	0	0
Not completed	8	8	8
Premature termination of the study	7	7	8
Serious adverse event	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BAY1093884 100mg
Reporting group description:	
Subjects received BAY1093884 100 mg once a week until premature termination of the study	
Reporting group title	BAY1093884 225mg
Reporting group description:	
Subjects received BAY1093884 225 mg once a week until premature termination of the study	
Reporting group title	BAY1093884 400mg
Reporting group description:	
Subjects received BAY1093884 400mg once a week until premature termination of the study	

Reporting group values	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg
Number of subjects	8	8	8
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	44.0	43.5	43.1
standard deviation	± 14.5	± 15.6	± 5.9
Gender Categorical Units: Subjects			
Female	0	0	0
Male	8	8	8
Race Units: Subjects			
Asian	2	2	2
Black or African American	0	0	1
White	6	6	5

Reporting group values	Total		
Number of subjects	24		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	0		
Male	24		
Race Units: Subjects			
Asian	6		

Black or African American	1		
White	17		

End points

End points reporting groups

Reporting group title	BAY1093884 100mg
Reporting group description:	
Subjects received BAY1093884 100 mg once a week until premature termination of the study	
Reporting group title	BAY1093884 225mg
Reporting group description:	
Subjects received BAY1093884 225 mg once a week until premature termination of the study	
Reporting group title	BAY1093884 400mg
Reporting group description:	
Subjects received BAY1093884 400mg once a week until premature termination of the study	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects with at least one intake of study drug	

Primary: Number of subjects with drug-related treatment-emergent adverse events

End point title	Number of subjects with drug-related treatment-emergent adverse events[1]

End point description:

An adverse event (AE) was any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject in the study. Any bleeding event occurring during the study was not documented as an AE because this event was planned to be captured in the assessment of efficacy. AEs occurring after the first administration of study drug and up to and including 30 days after the last administration of study drug were defined as treatment-emergent AEs (TEAEs). Drug-related TEAEs were TEAEs that had "reasonable causal relationship" to the study treatment decided by the investigators.

End point type	Primary

End point timeframe:

After the first administration of study drug and up to and including 30 days after the last administration of study drug

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.

End point values	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[2]	8[3]	8[4]	
Units: Subjects	1	4	5	

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with serious treatment-emergent adverse events

End point title	Number of subjects with serious treatment-emergent adverse events[5]

End point description:

A serious adverse event (SAE) was any untoward medical occurrence that at any dose was resulting in death, was lifethreatening, requires hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity. SAEs occurring after the first administration of study drug and up to and including 30 days after the last administration of study drug were defined as serious treatment-emergent AEs (TESAEs). Drug-related TESAEs were TESAEs that had "reasonable causal relationship" to the study treatment decided by the investigators.

End point type	Primary

End point timeframe:

After the first administration of study drug and up to and including 30 days after the last administration of study drug

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.

End point values	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[6]	8[7]	8[8]	
Units: Subjects				
TESAEs	1	2	1	
Drug-related TESAEs	0	2	1	

Notes:

[6] - SAF

[7] - SAF

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent adverse events of special interest

End point title	Number of subjects with treatment-emergent adverse events of special interest[9]

End point description:

Any thromboembolic or thrombotic microangiopathic event or any hypersensitivity reaction was an adverse event of special interest (AESI). AESIs occurring after the first administration of study drug and up to and including 30 days after the last administration of study drug were defined as treatment-emergent AESIs.

End point type	Primary

End point timeframe:

After the first administration of study drug and up to and including 30 days after the last administration of study drug

Notes:

[9] - 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.

End point values	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[10]	8[11]	8[12]	
Units: Subjects	0	2	1	

Notes:

[10] - SAF

[11] - SAF

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically relevant abnormalities in laboratory values

End point title	Number of subjects with clinically relevant abnormalities in laboratory values[13]

End point description:

"Clinically relevant "implied the presence of a clinical sign or symptom that required medical action.

End point type	Primary

End point timeframe:

After the first administration of study drug and up to and including 30 days after the last administration of study drug

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of this trial and due to the premature termination of the study, only descriptive statistics were performed.

End point values	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[14]	8[15]	8[16]	
Units: Subjects	0	0	0	

Notes:

[14] - SAF

[15] - SAF

[16] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first administration of study drug and up to and including 30 days after the last administration of study drug

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	BAY1093884 100mg

Reporting group description:

Subjects received BAY1093884 100 mg once a week until premature termination of the study

Reporting group title	BAY1093884 225mg

Reporting group description:

Subjects received BAY1093884 225 mg once a week until premature termination of the study

Reporting group title	BAY1093884 400mg

Reporting group description:

Subjects received BAY1093884 400 mg once a week until premature termination of the study

Serious adverse events	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paranasal sinus neoplasm			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (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
Nervous system disorders			
Transverse sinus thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Ischaemic stroke			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Eye disorders			
Retinal artery thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BAY1093884 100mg	BAY1093884 225mg	BAY1093884 400mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	6 / 8 (75.00%)	6 / 8 (75.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Paranasal sinus neoplasm			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injection site bruising			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	19
Injection site inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	9
Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	26	0
Application site inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Pharyngeal hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Investigations			

Fibrin D dimer increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Muscle strain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bone contusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	2 / 8 (25.00%)
occurrences (all)	0	3	3

Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Hypofibrinogenaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tooth development disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Perianal erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Hypoaesthesia oral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Anal pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	2
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
Haemarthrosis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Joint swelling			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0

Muscle haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Labyrinthitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	5 / 8 (62.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	5	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2018	Integrated protocol version 2.0 introduced the following changes: 1. Text describing the product updated to include most recent data from the ongoing First in Man Phase 1 study; 2. Dose escalation criteria and safety rules between cohorts added in addition to those already described within cohorts/subjects; 3. Text added providing further detail on the role and responsibilities of the DMC; 4. Text added describing the rationale for fixed doses; 5. Communication plan added; 6. Text added stating that subjects may be replaced only if they have not withdrawn from the study for drug-related safety concerns; 7. Guidance added for use of bypassing agents to treat bleeds during treatment with BAY1093884; 8. Every 24-week visit changed to frequency of every 12 weeks; 9. Dose strength changed from "100 mg/mL" to "either 100 mg/mL or 150 mg/mL"; 10. Additional detail provided on the amount and type of safety, PK and PD data collected; 11. Local ECG added at Visits 3 – 7 and every 12 week visits; 12. LDL added to blood samples collected at Visit 2; 13. AE intensity should be graded according to NCI CTCAE version 5.0; 14. Section added describing reporting of non-approved medical device failures; 15. Section added to define DLTs for the study; 16. Lactate dehydrogenase and fibrinogen added to standard safety laboratory analyses; 17. Immunoglobulins would be collected for hypersensitivity reactions; 18. LDH added to central laboratory tests for thromboembolic and thrombotic microangiopathic events; 19. Section added to note that ECGs would be performed at PK visits; 20. Injection site reactions removed as separate endpoint, as these would be collected as part of regular AE reporting; 21. Note pertaining to DMC review of thromboembolic or thrombotic icroangiopathic events removed, as this was now described in new section.
12 February 2019	Integrated protocol version 3.0 introduced the following changes: 1. The visit schedule was updated to include an additional safety visit 6 weeks (± 1 day) after dose escalation; 2. Inclusion criterion 1 was modified to specify that subjects with inhibitors against FVIII or FIX also have undetectable FVIII or FIX levels; 3. Exclusion criterion 10 was modified to more accurately describe advanced liver disease.
05 April 2019	Integrated protocol version 4.0 introduced the following changes: Inclusion criterion 1 was modified to further specify that only subjects diagnosed with severe hemophilia, with or without inhibitors, are eligible.

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.

Acceptable safety and tolerability of multiple subcutaneous doses of befovacimab in subjects with hemophilia A or B with or without inhibitors was not demonstrated, prompting early termination of the study.

Notes: