Clinical trial results:
A Phase 2a Multiple Dose “Basket Design” Study Of The Safety, Tolerability, And Pharmacologic Activity Of BT200 In Patients With Hereditary Bleeding Disorders

Summary

EudraCT number	2020-003807-32
Trial protocol	AT
Global end of trial date	24 August 2021

Results information

Result version number	v2 (current)
This version publication date	11 May 2022
First version publication date	20 April 2022
Version creation reason	• Correction of full data set Data addition

Trial information

Trial identification

Sponsor protocol code	BT200-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04677803
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienn, Austria, 1090
Public contact	Dept. of Clinical Pharmacology, Medical University of Vienna, 0043 140400298190, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Dept. of Clinical Pharmacology, Medical University of Vienna, 0043 140400298190, klin-pharmakologie@meduniwien.ac.at

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	31 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2021
Global end of trial reached?	Yes
Global end of trial date	24 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to obtain clinical proof of mechanism for BT200 in one or more hereditary bleeding disorders.

Protection of trial subjects:

Prior to any trial-related activity, the Investigator or an authorized physician gave the patient oral and written information about the trial in a form that the patient was able to read and to understand. A voluntary, signed and dated Informed Consent Form was to be obtained from the patient prior to any trial-related activity. The patient had to consent to participate after the nature, scope, and possible consequences of the clinical trial were explained in a form understandable to the patient. It was also explained to the patient that he/she was free to refuse to enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the Investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 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	Austria: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	25

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Hereditary bleeding disorder
Congenital hemophilia A w/o inhibitors on a prophylactic treatment regimen
Heterozygous carriers of hem. A with subnormal FVIII levels
Von Willebrand disease (VWD) Type 1
VWD type IIb (also known as "VWD Type 2b" or "type 2B VWD")
VWD Type 3 under subst. therapy
Acquired von Willebrand Syndrome w/o spec inhib.

Pre-assignment

Screening details:

Patients underwent the Screening Visit within 28 days prior to dosing on Day 0. All patients were to be dosed with a subcutaneous (SC) injection of 3 mg BT200 on Days 0 and 4. Thereafter, doses of the weekly SC injections were to be titrated between 3 and 9 mg based on the patient's response.

Period 1

Period 1 title	Overall trial (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	Hemophilia A Mild/Mod

Arm description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Arm type	Active comparator
Investigational medicinal product name	BT200
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.

Arm title	Hemophilia A Severe

Arm description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Arm type	Active comparator
Investigational medicinal product name	BT200
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.

Arm title	VWD Type 2b

Arm description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD type IIb: titration until normalization of platelet count and/or FVIII activity level

Arm type	Active comparator
Investigational medicinal product name	BT200
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.

Arm title	VWD Type 3

Arm description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD Type 3 under substitution therapy: titration only between 3 and 6 mg

Arm type	Active comparator
Investigational medicinal product name	BT200
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.

Arm title	aVWS

Arm description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance

below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
aVWS: titration until normalization of FVIII activity

Arm type	Active comparator
Investigational medicinal product name	BT200
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.

Number of subjects in period 1	Hemophilia A Mild/Mod	Hemophilia A Severe	VWD Type 2b
Started	10	9	5
Completed	10	9	5
Not completed	0	0	0
Lost to follow-up	-	-	-

Number of subjects in period 1	VWD Type 3	aVWS
Started	1	1
Completed	0	1
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Hemophilia A Mild/Mod

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Reporting group title	Hemophilia A Severe

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Reporting group title	VWD Type 2b

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD type IIb: titration until normalization of platelet count and/or FVIII activity level

Reporting group title	VWD Type 3

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD Type 3 under substitution therapy: titration only between 3 and 6 mg

Reporting group title	aVWS

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
aVWS: titration until normalization of FVIII activity

Reporting group values	Hemophilia A Mild/Mod	Hemophilia A Severe	VWD Type 2b
Number of subjects	10	9	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	9	4
From 65-84 years	0	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	4	0	2
Male	6	9	3

Reporting group values	VWD Type 3	aVWS	Total
Number of subjects	1	1	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	25
From 65-84 years	0	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	1	7
Male	1	0	19

Subject analysis sets

Subject analysis set title	Hemophilia A Overall
Subject analysis set type	Full analysis

Subject analysis set description:

Blood samples for the determination of plasma concentrations were collected on Days 0, 4, 7, 14, 21, 28, 35, 42, 49 and 56 (EOS Visit). On dosing days, the sample was collected prior to administration of IMP.
The concentration of BT200 which is required to produce a 2-fold increase in FVIIIc activity was calculated to be in the range from 368 to 508 ng/mL, and the concentration of BT200 which would be required to produce a 2-fold increase in the VWF Ag level was calculated to be in the range from 459 to 649 ng/mL. Both of these thresholds were readily achieved after 6 doses of BT200 in all disease entities.Comment: Type 1 (0 subjects), 3 (1 subject) and aVWS (1 subject) were not analyzed.

Subject analysis set title	VWD Type IIb Overall
Subject analysis set type	Full analysis

Subject analysis set description:

Blood samples for the determination of plasma concentrations were collected on Days 0, 4, 7, 14, 21, 28, 35, 42, 49 and 56 (EOS Visit). On dosing days, the sample was collected prior to administration of IMP.
The concentration of BT200 which is required to produce a 2-fold increase in FVIIIc activity was calculated to be in the range from 368 to 508 ng/mL, and the concentration of BT200 which would. be required to produce a 2-fold increase in the VWF Ag level was calculated to be in the range from 459 to 649 ng/mL. Both of these thresholds were readily achieved after 6 doses of BT200 in

all disease entities.

Reporting group values	Hemophilia A Overall	VWD Type IIb Overall	
Number of subjects	17	5	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	17	4	
From 65-84 years	0	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	4	2	
Male	13	3	

End points

End points reporting groups

Reporting group title	Hemophilia A Mild/Mod

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Reporting group title	Hemophilia A Severe

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
Hemophilia A: titration until largest possible increase in FVIII activity before PFA-100® CADP-CT increased to 150 seconds. No up-titration from 3 mg was foreseen in severe hemophilia patients on on-demand therapy.

Reporting group title	VWD Type 2b

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD type IIb: titration until normalization of platelet count and/or FVIII activity level

Reporting group title	VWD Type 3

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
VWD Type 3 under substitution therapy: titration only between 3 and 6 mg

Reporting group title	aVWS

Reporting group description:

On Day 0 and Day 4 each patient was to receive a single SC injection of 3 mg of BT200. On Days 7, 14, 21, and 28, the BT200 dose was to be titrated between 3 mg and 9 mg using the guidance below. It was anticipated that dose adjustments were to be performed in 2-3 mg steps. The 9-mg dose was only to be applied on Day 21-28 under exceptional circumstances, e.g. if no relevant changes in PD and safety parameters were observed.
aVWS: titration until normalization of FVIII activity

Subject analysis set title	Hemophilia A Overall
Subject analysis set type	Full analysis

Subject analysis set description:

Blood samples for the determination of plasma concentrations were collected on Days 0, 4, 7, 14, 21, 28, 35, 42, 49 and 56 (EOS Visit). On dosing days, the sample was collected prior to administration of IMP.
The concentration of BT200 which is required to produce a 2-fold increase in FVIIIc activity was calculated to be in the range from 368 to 508 ng/mL, and the concentration of BT200 which would be required to produce a 2-fold increase in the VWF Ag level was calculated to be in the range from 459 to 649 ng/mL. Both of these thresholds were readily achieved after 6 doses of BT200 in all disease entities.Comment: Type 1 (0 subjects), 3 (1 subject) and aVWS (1 subject) were not analyzed.

Subject analysis set title	VWD Type IIb Overall
Subject analysis set type	Full analysis

Subject analysis set description:

Blood samples for the determination of plasma concentrations were collected on Days 0, 4, 7, 14, 21, 28, 35, 42, 49 and 56 (EOS Visit). On dosing days, the sample was collected prior to administration of IMP.
The concentration of BT200 which is required to produce a 2-fold increase in FVIIIc activity was calculated to be in the range from 368 to 508 ng/mL, and the concentration of BT200 which would. be required to produce a 2-fold increase in the VWF Ag level was calculated to be in the range from 459 to 649 ng/mL. Both of these thresholds were readily achieved after 6 doses of BT200 in all disease entities.

Primary: FVIIIc activity change from Baseline to Day 35

End point title	FVIIIc activity change from Baseline to Day 35[1]

End point description:

End point type	Primary

End point timeframe:

Baseline to Day 35

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: 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. Either resolve this issue or provide a justification

End point values	Hemophilia A Overall	VWD Type IIb Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: fold change from Baseline				
arithmetic mean (standard error)	5.29 (± 141.1)	2.21 (± 24.0)		

Statistical analyses

No statistical analyses for this end point

Primary: FVIIIc Observed activity level at Day 35

End point title	FVIIIc Observed activity level at Day 35[2]

End point description:

End point type	Primary

End point timeframe:

Baseline to Day 35

Notes:

[2] - 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: 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. Either resolve this issue or provide a justification

End point values	Hemophilia A Overall	VWD Type IIb Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: percent				
arithmetic mean (standard error)	26.5 (± 94.1)	151 (± 26.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment Period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0
Reporting groups	
Reporting group title	Overall

Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 26 (65.38%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
General disorders and administration site conditions			

Injection site reaction subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1		
Injury, poisoning and procedural complications Subcutaneous haematoma subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Cardiac disorders Tachycardia			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 3 / 26 (11.54%) 5		
Blood and lymphatic system disorders Lymphangiopathy subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrointestinal haemorrhage subjects affected / exposed occurrences (all) Gingival bleeding subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Tongue haemorrhage subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 1 / 26 (3.85%) 1 3 / 26 (11.54%) 3 1 / 26 (3.85%) 1 1 / 26 (3.85%) 2		
Skin and subcutaneous tissue disorders			

Eczema subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Haemarthrosis subjects affected / exposed occurrences (all) Muscle haemorrhage subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Soft tissue haemorrhage subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 3 / 26 (11.54%) 6 1 / 26 (3.85%) 1 1 / 26 (3.85%) 2 1 / 26 (3.85%) 1		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Tooth infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1		
Metabolism and nutrition disorders			

Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported