Clinical trial results:
A Long-Term Follow-up Study to Evaluate the Safety, Tolerability, and Efficacy of Adeno-Associated Virus (AAV) rh10-Mediated Gene Transfer of Human Factor IX in Adults With Moderate/Severe to Severe Hemophilia B

Summary

EudraCT number	2016-003430-25
Trial protocol	GB
Global end of trial date	06 December 2021

Results information

Result version number	v1 (current)
This version publication date	16 December 2022
First version publication date	16 December 2022

Trial information

Trial identification

Sponsor protocol code	101HEMB02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02971969
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 16543

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, California , United States, 94949
Public contact	Patient Advocacy, Ultragenyx Pharmaceutical, Inc., +1 415 756-8657, Trialrecruitment@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical, Inc., +1 888 756-8657, Medinfo@ultragenyx.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	06 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term safety and efficacy of DTX101 following a single IV infusion in adults with moderate/severe to severe hemophilia B.

Protection of trial subjects:

The trial was designed, conducted, recorded, and reported in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigators made every effort to ensure that the study was conducted in full conformance with Helsinki principles, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, current Food and Drug Administration (FDA) regulations, EU Clinical Trial Directive 2001/20/EC, and local ethical and regulatory requirements. Each investigator was thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in the protocol and Investigator's Brochure, prior to the initiation of the study. The method of obtaining and documenting informed consent and the contents of the informed consent form (ICF) complied with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act regulations, and all other applicable regulatory requirements. Investigators were responsible for preparing the ICF and submitting it to the Sponsor for approval prior to submission to the Institutional Review Board (IRB). All ICFs were written in regional language and contained the minimum elements for consent as mandated by the ICH guidelines. An IRB-approved ICF was provided by the Sponsor prior to initiation of the study. Investigators obtained signed written informed consent from each potential study subject prior to the conduct of any study procedures and after the methods, objectives, requirements, and potential risks of the study were fully explained to each potential subject. Consent for participation could be withdrawn at any time for any reason by the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2017
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	United Kingdom: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	6
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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in Study 101HEMB02 after completing Study 101HEMB01 (EudraCT number 2015-001486-67), defined as completing visits through Week 52 (Cohort 1) or Week 44 (Cohort 2). Subjects were followed in Study 101HEMB02 for at least 4 years, for a total of at least 5 years from the time of DTX101 administration.

Pre-assignment

Screening details:

After providing informed consent, the subject completed Day 0 assessments and the Investigator determined the subject's eligibility to participate in the study. The Day 0 Visit could coincide with the Study 101HEMB01 Week 52 Visit for subjects in Cohort 1 or the Study 101HEMB01 Week 44 Visit for subjects in Cohort 2.

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	Cohort 1

Arm description:

Subjects enrolled in Study 101HEMB02 who received a single intravenous (IV) infusion of DTX101 during Study 101HEMB01 at a dose level of 1.6 × 10^12 GC/kg . No DTX101 was administered during Study 101HEMB02.

Arm type	No Intervention
Investigational medicinal product name	DTX101
Investigational medicinal product code	
Other name	non-replicating recombinant AAVrh10 encoding human FIX (hFIX), AAVrh10FIX
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

No DTX101 was administered during Study 101HEMB02.

Arm title	Cohort 2

Arm description:

Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of 5.0 × 10^12 GC/kg. No DTX101 was administered during Study 101HEMB02.

Arm type	No Intervention
Investigational medicinal product name	DTX101
Investigational medicinal product code	
Other name	non-replicating recombinant AAVrh10 encoding human FIX (hFIX), AAVrh10FIX
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

No DTX101 was administered during Study 101HEMB02.

Number of subjects in period 1	Cohort 1	Cohort 2
Started	3	3
Completed	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Subjects enrolled in Study 101HEMB02 who received a single intravenous (IV) infusion of DTX101 during Study 101HEMB01 at a dose level of 1.6 × 10^12 GC/kg . No DTX101 was administered during Study 101HEMB02.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of 5.0 × 10^12 GC/kg. No DTX101 was administered during Study 101HEMB02.	

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	3	3	6
Age categorical Units: Subjects			
Adults (18-64 years)	2	3	5
From 65-84 years	1	0	1
Age continuous Units: years			
arithmetic mean	60.3	42.7	
standard deviation	± 9.29	± 11.85	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	3	6
Ethnicity Units: Subjects			
Not Hispanic or Latino	3	2	5
Not Applicable	0	1	1
Race Units: Subjects			
White	3	3	6
Factor IX (FIX) Activity			
The documented history or measurement before the 101HEMB01 study Day 0 Visit following the appropriate washout was used for the Baseline FIX activity level. As determined by the activated partial thromboplastin time clot-based assay.			
Units: IU/dL			
arithmetic mean	1.67	0.87	
standard deviation	± 0.58	± 0.71	-

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Subjects enrolled in Study 101HEMB02 who received a single intravenous (IV) infusion of DTX101 during Study 101HEMB01 at a dose level of 1.6 × 10^12 GC/kg . No DTX101 was administered during Study 101HEMB02.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of 5.0 × 10^12 GC/kg. No DTX101 was administered during Study 101HEMB02.	

Primary: Number of Subjects With Adverse Events (AEs), Treatment-Related Adverse Events (TEAEs), and Serious AEs (SAEs)

End point title	Number of Subjects With Adverse Events (AEs), Treatment-Related Adverse Events (TEAEs), and Serious AEs (SAEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a subject enrolled into this study (from the time the subject signed the informed consent form until his or her exit from the study), regardless of its causal relationship to study treatment. A TEAE was defined as any event not present before exposure to study product or any event already present that worsened in severity or increased in frequency after exposure to study product. The relationship of TEAE to study product was categorized as "unrelated," "possibly related," "probably related," or "definitely related." For summaries by relationship, AEs with a missing relationship were considered to be "possibly related." For summaries by the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 grade (Grades 1 [mild] to 5 [death]), AEs missing a CTCAE grade were considered to be CTCAE Grade 3.

End point type	Primary

End point timeframe:

Follow-up for a median overall duration of 1488.0 days

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: Descriptive statistics planned per protocol are presented in the data table.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: subjects				
Any TEAE	3	3		
Any serious TEAE	1	1		
Any TEAE with Grade ≥ 3	1	1		
Any related TEAE	1	0		
Any related serious TEAE	0	0		
Any related TEAE with Grade ≥ 3	0	0		
Any TEAE leading to study discontinuation	0	0		
Any AE leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in FIX Activity at Week 208/216

End point title	Change from Baseline in FIX Activity at Week 208/216[2]

End point description:

As determined by the activated partial thromboplastin time clot-based assay. Change from Baseline = Postbaseline value – Baseline value. For the change from Baseline, only subjects with a value at both the Baseline Visit and the specific postbaseline visit were included.

End point type	Primary

End point timeframe:

Baseline (predose on Day 0 in Study 101HEMB01), Week 208 (Cohort 1)/216 (Cohort 2) ± 14 days

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: Statistics planned per protocol are presented in the data table.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[3]	3		
Units: IU/dL				
arithmetic mean (standard deviation)	64.0 (± 99999)	6.80 (± 5.803)		

Notes:

[3] - 99999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FIX Activity Over Time

End point title	Change from Baseline in FIX Activity Over Time

End point description:

As determined by the activated partial thromboplastin time clot-based assay. Change from Baseline = Postbaseline value – Baseline value. For the change from Baseline, only subjects with a value at both the Baseline Visit and the specific postbaseline visit were included.

End point type	Secondary

End point timeframe:

Baseline (predose on Day 0 in Study 101HEMB01), Day 0, Weeks 13, 26, 52, 104, 156, 208 (Cohort 1)/216 (Cohort 2) ± 14 days

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[4]	3[5]		
Units: IU/dL				
arithmetic mean (standard deviation)				
Change at follow-up Day 0; n=3, 3	15.00 (± 23.388)	22.13 (± 1.305)		
Change at follow-up Week 13; n=2, 0	1.00 (± 1.414)	99999 (± 99999)		

Change at follow-up Week 26; n=3, 2	4.33 (± 5.859)	13.95 (± 12.799)		
Change at follow-up Week 52; n=3, 2	5.67 (± 9.866)	2.25 (± 2.475)		
Change at follow-up Week 104; n=3, 3	12.00 (± 17.321)	11.80 (± 7.744)		
Change at follow-up Week 156; n=2, 3	8.00 (± 8.485)	13.80 (± 6.883)		
Change at follow-up Week 208; n=1, 0	64.00 (± 999999)	99999 (± 99999)		
Change at follow-up Week 216; n=0, 3	99999 (± 99999)	6.80 (± 5.803)		

Notes:

[4] - 99999=not applicable (0 subjects); 999999=not applicable (1 subject)

[5] - 99999=not applicable (0 subjects)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Follow-up for a median overall duration of 1488.0 days

Adverse event reporting additional description:

Events presented below are treatment-emergent adverse events, defined as any event not present before exposure to study product or any event already present that worsened in severity or increased in frequency after exposure to study product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of 1.6 × 10^12 GC/kg . No DTX101 was administered during Study 101HEMB02.

Reporting group title	Cohort 2

Reporting group description:

Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of 5.0 × 10^12 GC/kg. No DTX101 was administered during Study 101HEMB02.

Reporting group title	Total

Reporting group description:

Subjects enrolled in Study 101HEMB02 who received a single IV infusion of DTX101 during Study 101HEMB01 at a dose level of either 1.6 × 10^12 GC/kg or 5.0 × 10^12 GC/kg. No DTX101 was administered during Study 101HEMB02.

Serious adverse events	Cohort 1	Cohort 2	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Renal and urinary disorders			
Haematuria	Additional description: Grade 3, coded using Common Terminology Criteria for Adverse Events, Version 4.03.		
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric Obstruction	Additional description: Grade 3, coded using Common Terminology Criteria for Adverse Events, Version 4.03.		

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain	Additional description: Grade 3, coded using Common Terminology Criteria for Adverse Events, Version 4.03.		
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 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	Cohort 1	Cohort 2	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Investigations			
Blood Urine Present			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	3	4
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Traumatic Haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	3
Traumatic Haemorrhage			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	5 / 6 (83.33%)
occurrences (all)	3	10	13
Nervous system disorders			
Neuropathy Peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1

Blood and lymphatic system disorders			
Spontaneous Haemorrhage			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	4 / 6 (66.67%)
occurrences (all)	34	18	52
General disorders and administration site conditions			
Fatigue	Additional description: Considered by the Investigator to be possibly related to study drug.		
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	2
Pain In Extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Infections and infestations			
Corona Virus Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Influenza			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Pneumonia Viral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2017	• Reduced the number of global study sites from up to 14 to up to 5 and reduced the sample size from approximately 12 to 18 to up to 6 subjects (Section 3.2). • Added a Week 216 time point (End of Study) for subjects enrolled in Cohort 2 to ensure all subjects are followed for safety for at least 4 years (Section 2, 3.2). • Increased the visit window for all visits after Day 0 from ±7 days to ±14 days (Table 15-1 and globally). • Removed the secondary objective and endpoints, which included development of a cell-mediated response to FIX as determined by enzyme-linked immunospot (ELISPOT) assay and the responses to the EuroQol 5D 5-level version™ (EQ-5D-5L) and Haemophilia Specific Quality of Life (Haem-A-QoL) questionnaires. The associated assessments were also removed (Section 2, 3.2.2, 8.2, 10.2, Table 15-1). • Removed the exploratory endpoints of the development of a cell-mediated response to AAVrh10 as determined by ELISPOT assay. The associated assessments were also removed (Section 2, 10.3). • Clarified inclusion criterion #2 to require the completion of Cohort 1/Week 52 or Cohort 2/Week 44 visit in Study 101HEMB01 (Section 4.1). • Reduced the number of follow-up visits from every 13 weeks to Weeks 26 and 52 for the first year and yearly thereafter for safety and efficacy evaluations. The total follow-up duration was maintained at 4 years (Section 3.2, 3.2.2, Table 15-1). • Removed electrocardiogram measurements and urinalysis (Section 8.2, 8.2.3, Table 8-1, Table 15-1). • The recording of on-demand recombinant FIX replacement therapy use was changed from paper or electronic diary to recording as concomitant medications (Section 6.2, 8.1.3). • The recording of bleeding episodes was changed from paper or electronic diary to as adverse events (Section 8.1.2). • Interim analyses were changed from annually to on an ad hoc basis (Section 10.4.5).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported