



## Clinical trial results:

**A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) administered to adult patients with severe or moderately severe haemophilia B**

### Summary

EudraCT number	2013-005579-42
Trial protocol	DE DK NL
Global end of trial date	15 April 2021

### Results information

Result version number	v1 (current)
This version publication date	27 April 2022
First version publication date	27 April 2022

### Trial information

#### Trial identification

Sponsor protocol code	CT-AMT-060-01 (060-01)
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02396342
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	uniQure biopharma B.V.
Sponsor organisation address	Paasheuvelweg 25A, Amsterdam, Netherlands, 1105 BP
Public contact	Natascha Schillemans, uniQure biopharma B.V., +31 20 240 6022, n.schillemans@uniquire.com
Scientific contact	Natascha Schillemans, uniQure biopharma B.V., +31 20 240 6022, n.schillemans@uniquire.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 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2021
Global end of trial reached?	Yes
Global end of trial date	15 April 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate the safety of systemic administration of AAV5-hFIX, an adeno-associated viral vector containing a codon-optimized hFIX gene, to adult patients with severe or moderately severe haemophilia B.

Protection of trial subjects:

Protection of trial subjects:

Appropriate inclusion and exclusion criteria were applied.

An Independent Data Monitoring Committee was appointed to

- be informed on the research protocol, informed consent documents and data safety reporting plans and monitoring plan;
- review the study performance and safety data and make recommendation(s) to the Sponsor on further study conduct, including:
  - o initiation of second cohort,
  - o continuation of the trial,
  - o termination of the trial,
  - o modification to the trial;

by assessing the study progress, safety data and especially Suspected Unexpected Serious Adverse Reactions.

Background therapy:

Subjects will continue their usual FIX replacement therapy (on-demand and prophylactic), as applicable. However, for subjects on prophylactic FIX replacement therapy, prophylaxis will be tapered when endogenous production of FIX is anticipated to have reached adequate levels

Evidence for comparator:

Due to the nature of the disease in question it is not ethical to perform a placebo-controlled trial and no relevant active comparators exist. Based on this the trial is designed as an open-label and uncontrolled trial.

Actual start date of recruitment	02 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

<b>Subjects enrolled per age group</b>	
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)	7
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Screening for the trial began on 01-Nov-2014 and the first subject was consented on 10-Jun-2015. 12 subjects were screened for the study, including 2 screen failures. Recruitment concluded in May 2016 when 10 subjects were enrolled.

### Pre-assignment

Screening details:

FIH, Patients with congenital haemophilia B

Known severe FIX deficiency with plasma FIX activity level < 1% and a severe bleeding phenotype

Known moderately severe FIX deficiency with plasma FIX activity level between  $\geq 1\%$  and  $\leq 2\%$  and a severe bleeding phenotype

More than 150 previous exposure days of treatment with FIX protein

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	AAV5-hFIX Low Dose (Cohort 1)

Arm description:

AAV5-hFIX  $5 \times 10^{12}$  gc/kg intravenous single infusion

Arm type	Experimental
Investigational medicinal product name	AAV5-hFIX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AAV5-hFIX  $5 \times 10^{12}$  gc/kg intravenous single infusion

<b>Arm title</b>	AAV5-hFIX High Dose (Cohort 2)
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Arm description:

AAV5-hFIX  $2 \times 10^{13}$  gc/kg intravenous single infusion

Arm type	Experimental
Investigational medicinal product name	AAV5-hFIX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AAV5-hFIX  $2 \times 10^{13}$  gc/kg intravenous single infusion

<b>Number of subjects in period 1</b>	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)
Started	5	5
Completed	5	5

## Baseline characteristics

### Reporting groups

Reporting group title	AAV5-hFIX Low Dose (Cohort 1)
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Reporting group description:

AAV5-hFIX 5 × 10E12 gc/kg intravenous single infusion

Reporting group title	AAV5-hFIX High Dose (Cohort 2)
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Reporting group description:

AAV5-hFIX 2 × 10E13 gc/kg intravenous single infusion

Reporting group values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)	Total
Number of subjects	5	5	10
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)	2	5	7
From 65-84 years	3	0	3
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	60.2	38.2	
standard deviation	± 15.9	± 5.9	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	5	5	10

## End points

### End points reporting groups

Reporting group title	AAV5-hFIX Low Dose (Cohort 1)
Reporting group description: AAV5-hFIX 5 × 10E12 gc/kg intravenous single infusion	
Reporting group title	AAV5-hFIX High Dose (Cohort 2)
Reporting group description: AAV5-hFIX 2 × 10E13 gc/kg intravenous single infusion	

### Primary: Number of Participants with Adverse events

End point title	Number of Participants with Adverse events <sup>[1]</sup>
End point description: Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Primary
End point timeframe: From AMT-060 infusion through end of study (5 years post-dose).	

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: Only descriptive statistics were used for this endpoint.

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: adverse events				
number (not applicable)	5	5		

### Statistical analyses

No statistical analyses for this end point

### Secondary: FIX-replacement-therapy-free FIX activity

End point title	FIX-replacement-therapy-free FIX activity
End point description: FIX activity measured any time from 72 hours after latest FIX replacement therapy administration and until next administration of FIX replacement therapy. Only assessments performed more than 10 days after most recent FIX-replacement therapy administration included. Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe: From AMT-060 infusion through end of study (5 years post-dose).	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4 <sup>[2]</sup>		
Units: Percent FIX activity				
arithmetic mean (standard deviation)				
one-stage aPTT assay	7.43 (± 1.28)	6.60 (± 1.96)		
amidolytic/chromogenic assay	4.58 (± 2.88)	4.74 (± 1.43)		

Notes:

[2] - n=5 for amidolytic/chromogenic assay

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Annualized Bleeding Rate (ABR)

End point title	Total Annualized Bleeding Rate (ABR)
End point description:	
Annualized: Sum of post-treatment bleeding episodes divided by subjects' average number of years (365.25 days) from treatment start to until the data cutoff date. Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe:	
From AMT-060 infusion through end of study (5 years post-dose).	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5 <sup>[3]</sup>		
Units: bleeds/year/subject				
arithmetic mean (standard deviation)				
One Year Prior to Screening	14.40 (± 5.73)	4.00 (± 3.16)		
Post-tapering Period	5.39 (± 5.94)	0.71 (± 0.58)		

Notes:

[3] - n=4 for One Year Prior to Screening

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total consumption of FIX replacement therapy

End point title	Total consumption of FIX replacement therapy
End point description:	
Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe:	
From AMT-060 infusion through end of study (5 years post dose).	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: IU				
arithmetic mean (standard deviation)				
One year prior to screening	326532 (± 234900)	233778 (± 156873)		
Post-tapering period	252950 (± 222790)	85800 (± 84482)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Short Form-36 (SF-36) Quality of Life (QoL) scores

End point title	Change from Baseline in Short Form-36 (SF-36) Quality of Life (QoL) scores
End point description:	
Scores range from 0 to 100, with a higher score defining a more favorable health state. Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe:	
From AMT-060 infusion through the end of study (5 years post dose).	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: total score				
arithmetic mean (standard deviation)				
Physical Functioning	0.00 (± 10.00)	-7.00 (± 9.75)		
Role-Physical	-15.00 (± 8.39)	-10.00 (± 22.79)		
Bodily Pain	-9.00 (± 9.00)	1.20 (± 14.81)		
General Health	-0.80 (± 20.22)	-2.40 (± 8.99)		
Vitality	-11.25 (± 19.96)	-6.25 (± 12.50)		
Social Functioning	-20.00 (± 25.92)	-5.00 (± 14.25)		
Role-Emotional	-13.33 (± 27.39)	-10.00 (± 13.69)		

Mental Health	-13.00 ( $\pm$ 22.80)	-9.00 ( $\pm$ 12.94)		
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Vector DNA Stopped Shedding from Blood, Nasal Secretions, Saliva, Urine, Feces, and Semen

End point title	Time to Vector DNA Stopped Shedding from Blood, Nasal Secretions, Saliva, Urine, Feces, and Semen
End point description:	Used Full Analysis Set which was comprised of all dosed subjects.
End point type	Secondary
End point timeframe:	From AMT-060 infusion through end of study (5 years post dose).

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 <sup>[4]</sup>	5		
Units: Days				
arithmetic mean (standard deviation)				
Blood	508.8 ( $\pm$ 261.7)	705.4 ( $\pm$ 245.1)		
Nasal secretions	83.4 ( $\pm$ 41.7)	108.4 ( $\pm$ 66.0)		
Saliva	75.8 ( $\pm$ 38.4)	129.2 ( $\pm$ 48.9)		
Urine	46.4 ( $\pm$ 20.9)	82.0 ( $\pm$ 41.1)		
Feces	74.0 ( $\pm$ 25.7)	165.0 ( $\pm$ 68.9)		
Semen	227.8 ( $\pm$ 147.7)	157.2 ( $\pm$ 78.4)		

Notes:

[4] - n=4 for semen

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Developing Neutralizing antibodies to AAV5

End point title	Number of Subjects Developing Neutralizing antibodies to AAV5
End point description:	Used Full Analysis Set which was comprised of all dosed subjects.
End point type	Secondary
End point timeframe:	From AMT-060 infusion through end of study (5 years post dose).

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects				
number (not applicable)	5	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total IgG and IgM Antibody Titers to AAV5

End point title	Total IgG and IgM Antibody Titers to AAV5
End point description:	Used Full Analysis Set which was comprised of all dosed subjects.
End point type	Secondary
End point timeframe:	From AMT-060 infusion through end of study (5 years post dose).

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 <sup>[5]</sup>	5 <sup>[6]</sup>		
Units: Titer				
number (not applicable)				
IgG (subject 1)	79499	109350		
IgG (subject 2)	109350	109350		
IgG (subject 3)	109350	109350		
IgG (subject 4)	109350	107344		
IgG (subject 5)	109350	109350		
IgM (subject 1)	56	30071		
IgM (subject 2)	1321	20000		
IgM (subject 3)	557	6649		
IgM (subject 4)	11568	50		
IgM (subject 5)	809	50		

Notes:

[5] - For subjects with a titer of 109350 the actual titer is >109350.

[6] - For subjects with a titer of 109350 and 50, the actual titer is >109350 and <50.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with a Positive AAV5 capsid-specific T cell Response

End point title	Number of Subjects with a Positive AAV5 capsid-specific T cell Response
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End point description:

Specific AAV5 response (results >17 SFC/million Peripheral Blood Mononuclear Cells) were regarded as positive. Used Full Analysis Set which was comprised of all dosed subjects.

End point type	Secondary
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End point timeframe:

From AMT-060 infusion through 26 weeks post-dose.

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects				
number (not applicable)	1	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Antibodies to FIX

End point title	Number of Subjects with Antibodies to FIX
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End point description:

Used Full Analysis Set which was comprised of all dosed subjects.

End point type	Secondary
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End point timeframe:

From AMT-060 infusion through the end of study (5 years post dose).

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects				
number (not applicable)	1	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with FIX inhibitors

End point title	Number of Subjects with FIX inhibitors
End point description: Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe: From AMT-060 infusion through the end of study (5 years post dose).	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Clinically Significant Inflammatory markers: IL-1 $\beta$ , IL-2, IL-6, INF $\gamma$ , MCP-1

End point title	Number of Subjects with Clinically Significant Inflammatory markers: IL-1 $\beta$ , IL-2, IL-6, INF $\gamma$ , MCP-1
End point description: Used Full Analysis Set which was comprised of all dosed subjects.	
End point type	Secondary
End point timeframe: From AMT-060 infusion through 18 weeks post dose.	

End point values	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of subjects				
number (not applicable)	0	0		

### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

5 years post-dose

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	AAV5-hFIX Low Dose (Cohort 1)
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Reporting group description: -

Reporting group title	AAV5-hFIX High Dose (Cohort 2)
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Reporting group description: -

Serious adverse events	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Myelopathy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
Renal Colic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Ureteric			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	AAV5-hFIX Low Dose (Cohort 1)	AAV5-hFIX High Dose (Cohort 2)	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	
<b>Vascular disorders</b>			
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Lymphoedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
<b>General disorders and administration site conditions</b>			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Influenza like illness			
subjects affected / exposed	3 / 5 (60.00%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	

Peripheral swelling subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 2	
Malaise subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Drug ineffective subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)  Anxiety subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2  1 / 5 (20.00%) 1	1 / 5 (20.00%) 1  1 / 5 (20.00%) 1	
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all)  Haemoglobin decreased	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Transaminases increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood urine present			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	5	1	
Upper limb fracture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ulna fracture			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hand fracture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Bone contusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Injury			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Muscle strain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Arthropod bite subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Palpitations subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 5 (20.00%) 1	
Dizziness subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 5 (0.00%) 0	
Nervous system disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Blood and lymphatic system disorders Splenomegaly subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Ear and labyrinth disorders			

Vertigo positional subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Eye disorders			
Blepharitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Cataract subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Gastrointestinal disorders			
Dyspepsia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Food poisoning subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Large intestine polyp subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Irritable bowel syndrome			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrointestinal sounds abnormal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Actinic keratosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	
occurrences (all)	3	2	
Arthralgia			
subjects affected / exposed	3 / 5 (60.00%)	0 / 5 (0.00%)	
occurrences (all)	10	0	
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	2	3	
Musculoskeletal pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Groin pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Tenosynovitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Synovial cyst			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	3 / 5 (60.00%) 8	
Influenza subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 5 (0.00%) 0	
Eye infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 2	
Cellulitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Rhinitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Cystitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Pulpitis dental subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	

Oral herpes			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2015	<ul style="list-style-type: none"><li>-Options to adjust the tapering/discontinuation start and/or schedule of prophylactic FIX replacement therapy to be in the best interest of the individual subject</li><li>-Clarifications were made to the tapering/discontinuation algorithm</li><li>-Optional screening for NAbs against the vector, HIV, and Hepatitis B and C ahead of other screening visit assessments was added</li><li>-Clarifications were also made to the serum chemistry samples during Dosing Visit 7, SAE reporting requirements, and requirements for re-evaluation of screen failures</li></ul>
22 December 2015	<ul style="list-style-type: none"><li>-Implemented twice weekly local monitoring of liver enzymes (AST/ALT)</li><li>-Recommended the use of rescue corticosteroid treatment if, in the absence of alternative etiology, the ALT level increase was greater than 1.5 to 2 fold the baseline level</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported