



Clinical trial results:

A Phase I/II Open-Label Safety and Dose-Finding Study 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 | 2015-001486-67 |
| Trial protocol | GB BG |
| Global end of trial date | 18 October 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 November 2018 |
| First version publication date | 01 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 101HEMB01 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02618915 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Ultragenyx Pharmaceutical Inc. |
| Sponsor organisation address | 60 Leveroni Court, Novato, United States, California 94949 |
| Public contact | Patient Advocacy, Ultragenyx Pharmaceutical Inc., 415 483-8800, patientadvocacy@ultragenyx.com |
| Scientific contact | Medical Information, Ultragenyx Pharmaceutical Inc., 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 | 18 October 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

- To determine the safety of single ascending intravenous (IV) doses of DTX101 in adults with moderate/severe to severe hemophilia B.
- To establish a dose of DTX101 that achieves a peak plasma level of vector-derived factor IX (FIX) at 6 weeks after IV administration to allow further clinical development.

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 December 2015 |
| 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 States: 4 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 6 |
| EEA total number of subjects | 2 |

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: -

Pre-assignment

Screening details:

This study included a 30-day Screening period.

Period 1

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | DTX101, Cohort 1 |

Arm description:

a single peripheral intravenous (IV) infusion of 1.6×10^{12} genome copies (GC)/kg DTX101

| | |
|----------------------------------------|---------------------------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | DTX101 |
| Investigational medicinal product code | DTX101 |
| 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:

The dose of DTX101 to be administered was calculated using the subject's weight recorded at Screening.

| | |
|------------------|------------------|
| Arm title | DTX101, Cohort 2 |
|------------------|------------------|

Arm description:

a single peripheral IV infusion of 5.0×10^{12} GC/kg DTX101

| | |
|----------------------------------------|---------------------------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | DTX101 |
| Investigational medicinal product code | DTX101 |
| 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:

The dose of DTX101 to be administered was calculated using the subject's weight recorded at Screening.

| Number of subjects in period 1 | DTX101, Cohort 1 | DTX101, Cohort 2 |
|---------------------------------------|------------------|------------------|
| Started | 3 | 3 |
| Completed | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title | DTX101, Cohort 1 |
| Reporting group description: a single peripheral intravenous (IV) infusion of 1.6×10^{12} genome copies (GC)/kg DTX101 | |
| Reporting group title | DTX101, Cohort 2 |
| Reporting group description: a single peripheral IV infusion of 5.0×10^{12} GC/kg DTX101 | |

| Reporting group values | DTX101, Cohort 1 | DTX101, Cohort 2 | Total |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------|-------|
| Number of subjects | 3 | 3 | 6 |
| Age categorical | | | |
| Units: Subjects | | | |
| 18-49 years | 0 | 3 | 3 |
| 50-84 years | 3 | 0 | 3 |
| Gender categorical | | | |
| Hemophilia B is an X-linked recessive bleeding disorder that affects approximately 1 in 20,000 to 25,000 male births. Only male subjects were screened. | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 3 | 3 | 6 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 3 | 3 | 6 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Factor IX (FIX) Activity | | | |
| The documented history or measurement before the Day 0 visit following the appropriate washout was used for the baseline values of FIX activity. | | | |
| Units: IU/dL | | | |
| arithmetic mean | 1.67 | 0.87 | |
| standard deviation | ± 0.577 | ± 0.709 | - |

End points

End points reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title | DTX101, Cohort 1 |
| Reporting group description: a single peripheral intravenous (IV) infusion of 1.6×10^{12} genome copies (GC)/kg DTX101 | |
| Reporting group title | DTX101, Cohort 2 |
| Reporting group description: a single peripheral IV infusion of 5.0×10^{12} GC/kg DTX101 | |

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: up to 52 weeks after dosing (Cohort 1) or 44 weeks after dosing (Cohort 2) | |

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 are presented per protocol.

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: subjects | | | | |
| All TEAEs | 3 | 3 | | |
| All serious TEAEs | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in FIX Activity at Week 6

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title | Change From Baseline in FIX Activity at Week 6 ^[2] |
| End point description: Peak plasma level of FIX after IV administration as determined by the activated partial thromboplastin time (aPTT) clot-based assay. Change from baseline: postbaseline value – baseline value. For the change from baseline, only subjects with a value at both baseline visit and the specific postbaseline visit | |

were included.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 6

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: Mean (SD) statistics are presented in the data table, per protocol.

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: IU/dL | | | | |
| arithmetic mean (standard deviation) | 5.00 (± 1.732) | 9.80 (± 4.687) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

| | |
|-----------------|--------------------------|
| End point title | Annualized Bleeding Rate |
|-----------------|--------------------------|

End point description:

The number of bleeding episodes per subject was recorded, and the annualized number of bleeding episodes was calculated.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 to Week 52

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: bleeding episodes/year | | | | |
| arithmetic mean (standard deviation) | 8.7 (± 5.53) | 5.0 (± 1.00) | | |

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:

Peak plasma level of FIX after IV administration as determined by the aPTT clot-based assay. Change from baseline: postbaseline value – baseline value. For the change from baseline, only participants with a value at both baseline visit and the specific postbaseline visit were included. Subjects were not

required to stop prophylactic treatment with recombinant FIX until after Week 4 and may have been restarted on their prophylactic recombinant FIX treatment after Week 14.

| | |
|----------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 2, 4, 6, 8, 12, 16, 24, 32, 40, End of Study (Week 52 for Cohort 1, Week 44 for Cohort 2)/Early Withdrawal | |

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: IU/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 | 16.33 (± 14.503) | 10.13 (± 7.988) | | |
| Week 4 | 8.67 (± 7.234) | 14.47 (± 10.835) | | |
| Week 6 | 5.00 (± 1.732) | 9.80 (± 4.687) | | |
| Week 8 | 14.67 (± 17.786) | 11.80 (± 6.646) | | |
| Week 12 | 11.33 (± 4.933) | 5.80 (± 2.207) | | |
| Week 16 | 7.67 (± 3.215) | 5.47 (± 3.066) | | |
| Week 24 | 2.33 (± 1.528) | 2.47 (± 2.214) | | |
| Week 32 | 9.33 (± 11.846) | 10.13 (± 2.702) | | |
| Week 40 | 15.33 (± 23.965) | 12.80 (± 16.008) | | |
| End of Study/Early Withdrawal | 1.67 (± 0.577) | 22.47 (± 1.380) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized FIX Replacement Therapy

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | Annualized FIX Replacement Therapy |
| End point description: | |
| The use of on-demand FIX replacement therapy was recorded by dose (IU/kg) administered, and the annualized use of FIX replacement therapy was calculated. Subjects were not required to stop prophylactic treatment with recombinant FIX until after Week 4 and may have been restarted on their prophylactic recombinant FIX treatment after Week 14. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 52 | |

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|--------------------------------------|---------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 ^[3] | 3 ^[4] | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 350115.2 (± 522106.19) | 64246.5 (± 805.34) | | |

Notes:

[3] - All subjects who received any amount of DTX101.

[4] - All subjects who received any amount of DTX101.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralizing Antibodies to FIX (FIX Inhibitor)

| | |
|-----------------|------------------------------------------------------------------------|
| End point title | Number of Subjects With Neutralizing Antibodies to FIX (FIX Inhibitor) |
|-----------------|------------------------------------------------------------------------|

End point description:

The development of neutralizing antibodies to FIX (FIX inhibitor), as determined by a Bethesda assay. A value of < 0.3 inhibitor units was considered to be no neutralizing antibodies.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 0 (predose), Weeks 6, 8, 16, 32, 40, End of Study (Week 52 for Cohort 1, Week 44 for Cohort 2)/Early Withdrawal

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: subjects | | | | |
| Day 0 (predose) | 0 | 0 | | |
| Week 6 | 0 | 0 | | |
| Week 8 | 0 | 0 | | |
| Week 16 | 0 | 0 | | |
| Week 32 | 0 | 0 | | |
| Week 40 | 0 | 0 | | |
| End of Study/Early Withdrawal | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Cell-Mediated Immune Response to FIX

| | |
|-----------------|--------------------------------------------------------------|
| End point title | Number of Subjects With Cell-Mediated Immune Response to FIX |
|-----------------|--------------------------------------------------------------|

End point description:

The development of a cell-mediated immune response to FIX, as determined by enzyme-linked

immunospot assay (ELISPOT).

| | |
|-----------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 0 (predose), Weeks 6, 8, 12, 16, 32, 40, 48, End of Study (Week 52 for Cohort 1, Week 44 for Cohort 2)/Early Withdrawal | |

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: subjects | | | | |
| Day 0 (predose) | 0 | 0 | | |
| Week 6 | 0 | 0 | | |
| Week 8 | 0 | 0 | | |
| Week 12 | 0 | 0 | | |
| Week 16 | 0 | 0 | | |
| Week 32 | 0 | 0 | | |
| Week 40 | 0 | 0 | | |
| Week 48 | 0 | 0 | | |
| End of Study/Early Withdrawal | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Responding to the EuroQoL-50-5 Level (EQ-50-5L) Questionnaire

| | |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Number of Subjects Responding to the EuroQoL-50-5 Level (EQ-50-5L) Questionnaire |
|-----------------|----------------------------------------------------------------------------------|

End point description:

EQ-5D-5L is a standardized, subject-rated instrument for use as a measure of health outcomes. The EQ 5D-5L includes 2 components: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has "no problems" (1), "some problems" (2), or "severe problems" (3).

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| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0 predose), Weeks 24, 36, 48, End of Study/Early Withdrawal (up to Week 52)

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: subjects | | | | |
| Day 0 | 3 | 3 | | |
| Week 24 | 3 | 3 | | |
| Week 36 | 3 | 2 | | |
| Week 48 | 2 | 1 | | |
| End of Study/Early Withdrawal | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Responding to the Haemophilia-Specific Quality of Life Questionnaire

| | |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Number of Subjects Responding to the Haemophilia-Specific Quality of Life Questionnaire |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

The Haemophilia-Specific Quality of Life questionnaire asks subjects about their perceptions of their health and treatment. The questionnaire is divided into the following 10 dimensions: physical health, feelings, view of themselves, sports & leisure, work & school, dealing with hemophilia, treatment, future, family planning, and partnership & sexuality. Questions are based on a 5-point Likert-scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time). If the question does not apply to the subject, the "not applicable" response is allowed in 3 of the domains (sport & leisure, work & school, family planning). Positively worded items need to be re-coded and domains will be transformed ranging from 0 to 100; higher domain and total scores indicating a higher impairment of health-related quality of life.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0 predose), Weeks 24, 36, 48, End of Study/Early Withdrawal (up to Week 52)

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: subjects | | | | |
| Day 0 | 3 | 3 | | |
| Week 24 | 3 | 3 | | |
| Week 36 | 3 | 2 | | |
| Week 48 | 2 | 1 | | |
| End of Study/Early Withdrawal | 2 | 0 | | |

Statistical analyses

Secondary: Average Weekly Use of FIX Replacement Therapy

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| End point title | Average Weekly Use of FIX Replacement Therapy |
| End point description: | |
| The use of on-demand FIX replacement therapy was recorded by dose (IU/kg) administered and the average weekly use of FIX replacement therapy was calculated. Subjects were not required to stop prophylactic treatment with recombinant FIX until after Week 4 and may have been restarted on their prophylactic recombinant FIX treatment after Week 14. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Screening), Week 0 through Week 52 | |

| End point values | DTX101, Cohort 1 | DTX101, Cohort 2 | | |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 ^[5] | 3 ^[6] | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline; n=3, 3 | 9659.1 (± 12502.19) | 5037.2 (± 3502.95) | | |
| Week 0 to 2; n=2, 1 | 12120.0 (± 11144.00) | 5000.0 (± 9999) | | |
| Week 3 to 4; n=1, 1 | 24000.0 (± 9999) | 7000.0 (± 9999) | | |
| Week 5 to 6; n=2, 1 | 9068.5 (± 10611.55) | 3000.0 (± 9999) | | |
| Week 7 to 8; n=2, 0 | 5120.0 (± 1244.51) | 99999 (± 99999) | | |
| Week 9 to 10; n=1, 0 | 32000.0 (± 9999) | 99999 (± 99999) | | |
| Week 11 to 12; n=3, 0 | 8076.7 (± 10325.91) | 99999 (± 99999) | | |
| Week 13 to 14; n=1, 0 | 12000.0 (± 9999) | 99999 (± 99999) | | |
| Week 15 to 16; n=1, 0 | 16000.0 (± 9999) | 99999 (± 99999) | | |
| Week 17 to 18; n=1, 2 | 8000.0 (± 9999) | 3375.0 (± 883.88) | | |
| Week 19 to 20; n=1, 1 | 12000.0 (± 9999) | 8000.0 (± 9999) | | |
| Week 21 to 22; n=3, 0 | 7832.8 (± 3057.68) | 99999 (± 99999) | | |
| Week 23 to 24; n=2, 0 | 8782.5 (± 10207.09) | 99999 (± 99999) | | |
| Week 25 to 26; n=2, 2 | 8902.5 (± 4380.53) | 5445.0 (± 3952.73) | | |
| Week 27 to 28; n=2, 2 | 8120.0 (± 5487.15) | 4725.0 (± 1025.30) | | |
| Week 29 to 30; n=2, 2 | 12120.0 (± 11144.00) | 2250.0 (± 353.55) | | |
| Week 31 to 32; n=1, 2 | 28000.0 (± 9999) | 2750.0 (± 1767.77) | | |
| Week 33 to 34; n=1, 3 | 12000.0 (± 9999) | 2816.7 (± 1877.72) | | |

| | | | | |
|-----------------------|----------------------|--------------------|--|--|
| Week 35 to 36; n=1, 0 | 12000.0 (± 9999) | 99999 (± 99999) | | |
| Week 37 to 38; n=2, 2 | 4795.0 (± 4532.55) | 3500.0 (± 2828.43) | | |
| Week 39 to 40; n=2, 2 | 26795.0 (± 35645.25) | 2375.0 (± 883.88) | | |
| Week 41 to 42; n=1, 1 | 24000.0 (± 9999) | 1500.0 (± 9999) | | |
| Week 43 to 44; n=1, 1 | 20000.0 (± 9999) | 1750.0 (± 9999) | | |
| Week 45 to 46; n=1, 1 | 20000.0 (± 9999) | 5000.0 (± 9999) | | |
| Week 47 to 48; n=1, 1 | 20000.0 (± 9999) | 7500.0 (± 9999) | | |
| Week 49 to 50; n=1, 0 | 24000.0 (± 9999) | 99999 (± 99999) | | |
| Week 51 to 52; n=1, 0 | 20000.0 (± 9999) | 99999 (± 99999) | | |

Notes:

[5] - n=subjects with an assessment at given time point; 9999=not applicable (1 participant analyzed)

[6] - n=subjects with an assessment at given time point; 9999=1 subject analyzed; 99999=0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 52 weeks after dosing (Cohort 1) or 44 weeks after dosing (Cohort 2).

Adverse event reporting additional description:

TEAEs are presented. 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. Due to concerns related to subject re-identification in this study, events are presented by system organ class only.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | DTX101, Cohort 1 |
|-----------------------|------------------|

Reporting group description:

a single peripheral intravenous (IV) infusion of 1.6×10^{12} genome copies (GC)/kg DTX101

| | |
|-----------------------|------------------|
| Reporting group title | DTX101, Cohort 2 |
|-----------------------|------------------|

Reporting group description:

a single peripheral IV infusion of 5.0×10^{12} GC/kg DTX101

| Serious adverse events | DTX101, Cohort 1 | DTX101, Cohort 2 | |
|---------------------------------------------------|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal and connective tissue disorders | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | DTX101, Cohort 1 | DTX101, Cohort 2 | |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | |
| Investigations | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| Investigations subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 0 | 3 / 3 (100.00%) 3 | |
| Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all) | 2 / 3 (66.67%) 2 | 1 / 3 (33.33%) 1 | |
| Vascular disorders Vascular disorders subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | |
| Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 3 (33.33%) 1 | |
| General disorders and administration site conditions General disorders and administration site disorders subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 3 (33.33%) 1 | |
| Eye disorders Eye disorders subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 3 (33.33%) 1 | |
| Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 3 (66.67%) 2 | |
| Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| disorders | | | |
| Musculoskeletal and connective tissue disorders | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 3 (33.33%) | |
| occurrences (all) | 2 | 1 | |
| Infections and infestations | | | |
| Infections and infestations | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 June 2015 | <p>Protocol Amendment 1, Version 02:</p> <ul style="list-style-type: none">- The protocol was originally designed to seamlessly move from a Phase 1/2 (Part 1) into a larger registration study (Part 2). Part 2 has been removed from this study and will be a separate study. The text has been revised throughout the protocol to reflect this change.- Assessment of the subject's quality of life (QoL) following treatment with DTX101 was originally planned for Part 2 of the study. With the removal of Part 2, the QoL questionnaires have been included as a secondary endpoint in this dose-finding study.- The frequency of clinical chemistry samples to monitor liver function tests (LFTs) has been increased to occur approximately every 4 days for the first 12 weeks after DTX101 administration to ensure that any elevation in LFTs, potentially as a result of autoimmune hepatitis, are discovered quickly and adequately managed.- The sampling scheme monitoring for viral shedding has been increased from 3 weeks to 12 weeks.- The frequency of site visits over the first 12 weeks has been reduced from weekly to bi-weekly (Week 2 through Week 12).- In order to accommodate the increased frequency of clinical chemistry sampling, subjects will be seen at home by clinically trained and qualified personnel approximately every 4 days (unless a study visit is scheduled) to minimize the frequency of study visits.- Elevated liver function test results associated with potential autoimmune hepatitis and infusion site reactions are no longer designated as AEs of special interest. They will continue to be recorded as AEs/SAEs in the clinical database. |
| 29 July 2015 | <p>Protocol Amendment 2, version 03:</p> <ul style="list-style-type: none">- The no observed adverse event level (NOAEL) used to develop the rationale for the starting dose of DTX101 was originally determined from a non-Good Laboratory Practice (GLP) nonclinical toxicology study and reported as 1.35×10^{13} genome copies (GC)/kg. A GLP-compliant nonclinical toxicology study has recently been completed and the NOAEL has changed to 5.0×10^{12} GC/mL. The dosing rationale and safety margins for each of the proposed doses of DTX101 have been revised to reflect this change.- The development of AAVrh10 binding antibodies has been added as an exploratory endpoint.- The optimal biological dose has been updated to be the dose that achieves or is closest to achieving the target peak FIX activity of $\geq 20\%$ of normal.- Amendment 1 of the protocol added home visits to accommodate the increased frequency of clinical chemistry sampling. The language has been revised to allow subjects to either visit the clinic or have samples taken at home by clinically trained and qualified personnel.- The safety stopping criteria has been updated to clarify that the study will be suspended so that the results can be reviewed and any risks to subjects can be mitigated. |
| 03 September 2015 | <p>Protocol Amendment 3, version 04:</p> <ul style="list-style-type: none">- Exclusion Criterion 2 was revised so that subjects with alanine aminotransferase and aspartate aminotransferase elevations $> 2.0 \times$ the upper limit of normal will not be eligible for the study. This has been reduced from $> 3.0 \times$ the upper limit of normal.- Language has been added to reflect that an interim analysis will be performed once the last subject enrolled in the study has completed Week 6. |

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.

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| After review of the DTX101 Phase 1/2 clinical trial data, a decision was made to discontinue the development of DTX101. The discontinuation was not due to any safety concerns related to DTX101. |
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Notes: