Clinical trial results:
A Phase 1/2, Open-Label Safety and Dose-Finding Study of Adeno-Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Human Ornithine Transcarbamylase (OTC) in Adults with Late-Onset OTC Deficiency

Summary

EudraCT number	2016-001057-40
Trial protocol	GB ES
Global end of trial date	15 December 2021

Results information

Result version number	v1
This version publication date	26 December 2022
First version publication date	26 December 2022

Trial information

Trial identification

Sponsor protocol code	301OTC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02991144
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., +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	15 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 1/2, open-label, single arm, multicenter, safety and dose finding study of DTX301 in adults with late-onset OTC deficiency. The primary objective of the study is to determine the safety of single intravenous (IV) doses of DTX301.

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:

To mitigate hepatotoxicity and preserve transgene expression, liver function tests were closely monitored following DTX301 administration. In Cohorts 1 to 3, a reactive corticosteroid taper regimen was administered to control transient vector-induced hepatic effects. The Investigator, in conjunction with the Ultragenyx medical lead, considered starting corticosteroid treatment when a subject's alanine aminotransferase (ALT) level exceeded the upper limit of normal (ULN) and the ALT increase was considered by the Investigator to be related to DTX301.

[1 13C]sodium acetate (0.33 mmol/kg [27 mg/kg] dissolved in 60 mL of water) was administered orally as a tracer to measure the rate of ureagenesis. Sodium acetate is a naturally occurring sodium salt of acetic acid and is commonly used as a food additive (E262).

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
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	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	16
EEA total number of subjects	7

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 27 subjects were screened for the study, 16 of whom were enrolled. Of the 16 participants enrolled, 5 participants discontinued the study before receiving DTX301, and were not assigned to a treatment arm.

Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	11

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Adverse event: 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: DTX301 2.0 × 10^12 GC/kg

Arm description:

DTX301 (scAAV8OTC) 2.0 × 10^12 GC/kg administered as a single peripheral intravenous (IV) infusion.

Arm type	Experimental
Investigational medicinal product name	DTX301
Investigational medicinal product code	scAAV8OTC
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prior to clinical use, multiple DTX301 vials were thawed and aseptically diluted into sterile saline for IV infusion administration.

Arm title	Cohort 2: DTX301 6.0 × 10^12 GC/kg

Arm description:

DTX301 (scAAV8OTC) 6.0 × 10^12 GC/kg administered as a single peripheral IV infusion.

Arm type	Experimental
Investigational medicinal product name	DTX301
Investigational medicinal product code	scAAV8OTC
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prior to clinical use, multiple DTX301 vials were thawed and aseptically diluted into sterile saline for IV infusion administration.

Arm title	Cohort 3: DTX301 1.0 × 10^13 GC/kg

Arm description:

DTX301 (scAAV8OTC) 1.0 × 10^13 GC/kg administered as a single peripheral IV infusion.

Arm type	Experimental
Investigational medicinal product name	DTX301
Investigational medicinal product code	scAAV8OTC
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prior to clinical use, multiple DTX301 vials were thawed and aseptically diluted into sterile saline for IV infusion administration.

Arm title	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroid

Arm description:

Oral prednisone (or prednisolone), 60 mg tapered over 9 weeks, initiated before dosing with DTX301 (scAAV8OTC) and administered through Week 4. DTX301 (scAAV8OTC) 1.0x10^13 GC/kg administered as a single peripheral IV infusion.

Arm type	Experimental
Investigational medicinal product name	DTX301
Investigational medicinal product code	scAAV8OTC
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prior to clinical use, multiple DTX301 vials were thawed and aseptically diluted into sterile saline for IV infusion administration.

Investigational medicinal product name	Prophylactic Corticosteroid Taper Regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral prednisone [or oral prednisolone] 60 mg/day at least 5 days prior to DTX301 administration, tapered over 9 weeks.

Number of subjects in period 1[1]	Cohort 1: DTX301 2.0 × 10^12 GC/kg	Cohort 2: DTX301 6.0 × 10^12 GC/kg	Cohort 3: DTX301 1.0 × 10^13 GC/kg
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1[1]	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroid
Started	2
Completed	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 16 participants enrolled, 5 participants discontinued the study before receiving DTX301, and were not assigned to a treatment arm.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: DTX301 2.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 2.0 × 10^12 GC/kg administered as a single peripheral intravenous (IV) infusion.	
Reporting group title	Cohort 2: DTX301 6.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 6.0 × 10^12 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	Cohort 3: DTX301 1.0 × 10^13 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 1.0 × 10^13 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroid
Reporting group description:	
Oral prednisone (or prednisolone), 60 mg tapered over 9 weeks, initiated before dosing with DTX301 (scAAV8OTC) and administered through Week 4. DTX301 (scAAV8OTC) 1.0x10^13 GC/kg administered as a single peripheral IV infusion.	

Reporting group values	Cohort 1: DTX301 2.0 × 10^12 GC/kg	Cohort 2: DTX301 6.0 × 10^12 GC/kg	Cohort 3: DTX301 1.0 × 10^13 GC/kg
Number of subjects	3	3	3
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	32.3	27.7	26.7
standard deviation	± 11.06	± 1.15	± 7.09
Gender categorical			
Units: Subjects			
Female	1	2	2
Male	2	1	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	3	2	3
Race			
Units: Subjects			
Asian	1	0	0
White	2	3	3
Rate of Ureagenesis			
Rate of ureagenesis (as measured by the generation of [13C]urea over 4 hours; see Endpoint 2 for details). Baseline is defined as the average of all non-missing assessments taken before the study drug administration. If the absolute difference of results between Screening and Day 1 was ≥ 25% of normal rate of ureagenesis, then the screening value is defined as the baseline.			
Units: µmol*h/kg			
arithmetic mean	166.293	103.329	115.492
standard deviation	± 28.0167	± 76.9798	± 71.0753
Area Under the Curve From Time Zero to 24 Hours (AUC0 24) of Plasma Ammonia			

Baseline is defined as the Day -1 result. Measure Analysis Population Description: participants with a baseline assessment (n=1 for Cohort 3: DTX301 1.0 × 10^13 GC/kg) 99999 Explanation: 1 participant analyzed			
Units: µmol*h/L			
arithmetic mean	1831.78	2153.74	4444.76
standard deviation	± 1445.240	± 1406.173	± 99999

Reporting group values	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroid	Total	
Number of subjects	2	11	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	30.5		
standard deviation	± 13.44	-	
Gender categorical Units: Subjects			
Female	2	7	
Male	0	4	
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	2	10	
Race Units: Subjects			
Asian	0	1	
White	2	10	
Rate of Ureagenesis			
Rate of ureagenesis (as measured by the generation of [13C]urea over 4 hours; see Endpoint 2 for details). Baseline is defined as the average of all non-missing assessments taken before the study drug administration. If the absolute difference of results between Screening and Day 1 was ≥ 25% of normal rate of ureagenesis, then the screening value is defined as the baseline.			
Units: µmol*h/kg			
arithmetic mean	174.678		
standard deviation	± 210.9140	-	
Area Under the Curve From Time Zero to 24 Hours (AUC0 24) of Plasma Ammonia			
Baseline is defined as the Day -1 result. Measure Analysis Population Description: participants with a baseline assessment (n=1 for Cohort 3: DTX301 1.0 × 10^13 GC/kg) 99999 Explanation: 1 participant analyzed			
Units: µmol*h/L			
arithmetic mean	1834.39		
standard deviation	± 1091.019	-	

End points

End points reporting groups

Reporting group title	Cohort 1: DTX301 2.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 2.0 × 10^12 GC/kg administered as a single peripheral intravenous (IV) infusion.	
Reporting group title	Cohort 2: DTX301 6.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 6.0 × 10^12 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	Cohort 3: DTX301 1.0 × 10^13 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 1.0 × 10^13 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroid
Reporting group description:	
Oral prednisone (or prednisolone), 60 mg tapered over 9 weeks, initiated before dosing with DTX301 (scAAV8OTC) and administered through Week 4. DTX301 (scAAV8OTC) 1.0x10^13 GC/kg administered as a single peripheral IV infusion.	

Primary: Number of Participants With Adverse Events (AEs), Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and TEAEs Leading to Discontinuation

End point title	Number of Participants With Adverse Events (AEs), Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and TEAEs Leading to Discontinuation[1]

End point description:

AE: any untoward medical occurrence regardless of its causal relationship to study product. TEAE: any event not present before exposure to study product or any event already present that worsens in either intensity or frequency after exposure to study product. SAE: any event that results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; is an important medical event, according to the investigator. AE intensity was rated as Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life threatening), or 5 (death) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The relationship or association of the study product in causing or contributing to the AE was characterized as: unrelated; possible; probably; definite.

Safety Set: all participants who received DTX301.

End point type	Primary

End point timeframe:

AEs Prior to Dosing: From signing the informed consent form (ICF) to first dose of study drug. TEAEs: From first dose of study drug up to End of Study (Week 52).

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 for this endpoint.

End point values	Cohort 1: DTX301 2.0 × 10^12 GC/kg	Cohort 2: DTX301 6.0 × 10^12 GC/kg	Cohort 3: DTX301 1.0 × 10^13 GC/kg	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: participants				

Any AE prior to dosing	1	1	0	1
Any TEAE	3	3	3	2
Any serious TEAE	0	0	0	1
Any TEAE with grade >=3	0	0	0	1
Any study drug-related TEAE	2	1	3	2
Any TEAE related to corticosteroid regimen	1	0	1	1
Any hyperammonemic crisis-related TEAE	0	0	0	1
Any study drug-related serious TEAE	0	0	0	0
Any study drug-related TEAE with grade >=3	0	0	0	0
Any TEAE leading to study discontinuation	0	0	0	0
Any adverse event leading to death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Rate of Ureagenesis

End point title	Change From Baseline Over Time in Rate of Ureagenesis

End point description:

The change from baseline in the rate of ureagenesis (as measured by the generation of [13C]urea over 4 hours) as determined by gas chromatography mass spectrometry over time to 52 weeks after the IV administration of DTX301. Sodium acetate was used as a tracer to measure the rate of ureagenesis. Rate of ureagenesis was derived in the following manner:
1. Derive area under the curve from time zero to 240 minutes (AUC0-240min) of absolute 13C-urea (µmol/l/min) estimated by the linear trapezoidal rule
2. Derive percent of normal AUC0-240min of absolute 13C-urea by dividing AUC0-240min of absolute 13C-urea (µmol*min/L) by 669.56 µmol*min/L (i.e. the AUC0-240min of absolute 13C-urea for an adult control)
3. Derive rate of ureagenesis by multiplying % of normal AUC0-240min of absolute 13C-urea by 300 µmol*h/kg (i.e. the approximate rate of ureagenesis in healthy adults).

Safety Set: all participants who received DTX301.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Weeks 6, 12, 20, 24, End of Study (Week 52). AUC was derived based on the following time points: 0.5, 1, 1.5, 2, 3, and 4 hours postdose.

End point values	Cohort 1: DTX301 2.0 × 10^12 GC/kg	Cohort 2: DTX301 6.0 × 10^12 GC/kg	Cohort 3: DTX301 1.0 × 10^13 GC/kg	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: µmol*h/kg				
arithmetic mean (standard deviation)				
Change at Week 6	41.139 (± 83.3604)	46.857 (± 105.9147)	-29.017 (± 127.2471)	14.586 (± 17.3499)

Change at Week 12	2.363 (± 51.2516)	20.897 (± 56.9733)	7.544 (± 133.1715)	65.781 (± 33.9137)
Change at Week 20	32.929 (± 71.0500)	77.465 (± 67.1567)	-0.194 (± 112.5922)	67.103 (± 102.5409)
Change at Week 24	42.540 (± 136.5861)	65.513 (± 50.5169)	45.114 (± 147.5760)	63.854 (± 106.7694)
Change at End of Study (Week 52)	109.611 (± 171.0689)	114.446 (± 98.8701)	10.016 (± 47.9128)	128.023 (± 131.6469)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Area Under the Curve From Time Zero to 24 Hours (AUC0-24) of Plasma Ammonia

End point title	Change From Baseline Over Time in Area Under the Curve From Time Zero to 24 Hours (AUC0-24) of Plasma Ammonia

End point description:

Safety Set: all participants who received DTX301. n=Participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Weeks 6, 12, 24, End of Study (Week 52). AUC was derived based on predose (time 0) and approximately 2, 4, 8, 12, 16, 20, 24 hours (±5 minutes) postdose.

End point values	Cohort 1: DTX301 2.0 × 10^12 GC/kg	Cohort 2: DTX301 6.0 × 10^12 GC/kg	Cohort 3: DTX301 1.0 × 10^13 GC/kg	Cohort 4: DTX301 1.0x10^13 GC/kg + Prophylactic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3[2]	2
Units: µmol*h/L				
arithmetic mean (standard deviation)				
Change at Week 6; n=2, 3, 1, 2, 3	97.69 (± 104.381)	-1334.27 (± 1271.205)	-3790.83 (± 99999)	-1095.20 (± 785.719)
Change at Week 12; n=3, 3, 1, 2, 3	-264.07 (± 1471.172)	-1384.95 (± 1279.839)	-3827.36 (± 99999)	-1242.69 (± 931.242)
Change at Week 24; n=3, 3, 1, 2, 3	-252.54 (± 586.131)	-1065.48 (± 1024.167)	-3978.51 (± 99999)	-1276.25 (± 943.999)
Change at End of Study (Week 52); n=3, 2, 1, 2, 3	-381.54 (± 1116.898)	-387.02 (± 277.086)	-594.76 (± 99999)	-359.17 (± 1641.519)

Notes:

[2] - 99999=not calculated since 1 participant was analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events and serious adverse events: from first dose of study drug up to End of Study (Week 52).	
Adverse event reporting additional description:	
2 enrolled participants died before receiving DTX301, and were not assigned to a treatment arm.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	DTX301 2.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 2.0 × 10^12 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	DTX301 6.0 × 10^12 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 6.0 × 10^12 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	DTX301 1.0 × 10^13 GC/kg
Reporting group description:	
DTX301 (scAAV8OTC) 1.0 × 10^13 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroids
Reporting group description:	
Oral prednisone (or prednisolone), 60 mg tapered over 9 weeks, initiated before dosing with DTX301 (scAAV8OTC) and administered through Week 4. DTX301 (scAAV8OTC) 1.0x10^13 GC/kg administered as a single peripheral IV infusion.	
Reporting group title	Total
Reporting group description:	
All Participants	

Serious adverse events	DTX301 2.0 × 10^12 GC/kg	DTX301 6.0 × 10^12 GC/kg	DTX301 1.0 × 10^13 GC/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Metabolism and nutrition disorders			
Hyperammonaemic Crisis	Additional description: There were 2 serious adverse events of hyperammonaemic crisis that occurred in 1 subject postdosing.		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DTX301 1.0x10^13 GC/kg + Prophylactic	Total	

	Corticosteroids		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Metabolism and nutrition disorders			
Hyperammonaemic Crisis	Additional description: There were 2 serious adverse events of hyperammonaemic crisis that occurred in 1 subject postdosing.		
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DTX301 2.0 × 10^12 GC/kg	DTX301 6.0 × 10^12 GC/kg	DTX301 1.0 × 10^13 GC/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Catheter Site Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Feeling Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Feeling Jittery			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait Disturbance			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nasal Congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Upper-Airway Cough Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Claustrophobia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Phonophobia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2
Liver Function Test Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Liver Function Test Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Exposure To Sars-Cov-2			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	2
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuropathy Peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Somnolence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Gallbladder Polyp			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pain In Extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	DTX301 1.0x10^13 GC/kg + Prophylactic Corticosteroids	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	11 / 11 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 2 (50.00%)	3 / 11 (27.27%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Catheter Site Pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Feeling Abnormal			
subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Feeling Jittery			

subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Gait Disturbance			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nasal Congestion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oropharyngeal Pain			
subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Upper-Airway Cough Syndrome			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Claustrophobia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Irritability			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Phonophobia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	3	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Liver Function Test Increased			
subjects affected / exposed	2 / 2 (100.00%)	2 / 11 (18.18%)	
occurrences (all)	3	3	
Injury, poisoning and procedural complications			
Exposure To Sars-Cov-2			
subjects affected / exposed	2 / 2 (100.00%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 2 (100.00%)	5 / 11 (45.45%)	
occurrences (all)	10	14	
Hypoaesthesia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	

Neuropathy Peripheral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Somnolence			
subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	4	
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	4	4	
Retching			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Gallbladder Polyp			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hepatitis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 2 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Back Pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pain In Extremity			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	4	4	
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastroenteritis Viral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	1 / 2 (50.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Respiratory Tract Infection			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
Hypophosphataemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2016	• Added the rationale for defining hyperammonemia as an ammonia level ≥ 100 µmol/L • Increased the dosing interval between subjects in Cohort 1 and Cohort 2 from 7 days to 14 days and added the rationale for this change • Reversed the order of the secondary endpoints; designated the rate of ureagenesis as the main efficacy parameter to identify the DTX301 OBD • Updated the DTX301 dose levels for Dose 1 and Dose 2 • Decreased the number of inpatient visits • Changed the timing of tapering or discontinuing ammonia scavenger medication to after the Week 12 and Week 24 Visits • Revised the study stopping criteria • Updated Inclusion Criterion 2 with specific examples of testing to confirm OTC deficiency • Added Inclusion Criterion 5 to ensure subjects had stable OTC deficiency before receiving DTX301 • Combined Inclusion Criterion 10 with Exclusion Criterion 13 to create one criterion related to or pregnancy • Revised assessment time points for the rate of ureagenesis due to the decrease in inpatient visits; added the option to assess the rate of ureagenesis at any outpatient visit if clinically indicated • Revised the criteria for starting corticosteroids for suspected vector-induced hepatitis • Decreased the number of neuropsychological evaluations • Added clinical chemistry assessments at Weeks 18 and 22 • Removed text specifying that subjects would receive a prescribed diet during each inpatient stay and that the subject's prescribed diet may be adjusted
20 December 2016	• Expanded text regarding tapering of ammonia scavenger medication • Added a requirement for plasma ammonia level to be < 100 µmol/L prior to administration of neuropsychological tests and [1-13C]sodium acetate • Added text regarding repeat liver function testing to inform use of corticosteroids for possible vector-induced hepatitis • Added assessment of anti-OTC antibodies • Updated the sample type for ammonia assessments to plasma

07 February 2017	• Changed the timing of DMC review for each dose cohort from Week 6 to Week 12 • Added guidance for rescreening patients who fail screening • Added text to allow flexibility in the timing and sequence of assessments • Added text to specify that the Day 1 (predose) plasma ammonia level must be assessed within 12 hours or less before DTX301 administration • Added text to specify that, when a stopping rule is met, a substantial amendment needs to be approved by the regulatory authority to restart enrollment following DMC review • Added a definition of abstinence as a form of birth control • Deleted Inclusion Criterion 7 because tapering or discontinuing ammonia scavenger medications is not required • Corrected the anti-AAV8 neutralizing antibody titer in Exclusion Criterion 9 • Added assessment of liver function tests at the local laboratory (STAT samples) through Week 12 • Changed the ALT level for considering initiation of corticosteroids from 2.5 × ULN to > ULN and updated Exclusion Criterion 4 to reflect this change • Added additional assessments of cell-mediated immune response to AAV8 and OTC through Week 12 • Added text to allow subjects to rest during administration of neuropsychological tests and to explain the importance of assessing neuropsychological functioning long-term
11 June 2019	• Added a reference to another AAV gene therapy study using a prophylactic corticosteroid regimen • Removed outdated information regarding the DTX301 manufacturing process • Incorporated changes detailed in Addendum A to Amendment 3 (dated 02 March 2017), which updated Figure 3-1 Study Design to align with protocol text • Incorporated changes detailed in Addendum B (UK-specific) to Amendment 3 (dated 21 April 2017), which specified the timing of dosing for subjects at sites in the UK • Added details regarding enrolling additional subjects in Cohort 3 and subjects in Cohort 4 • Added a brief summary of safety results from the study • Added a reference to another AAV gene therapy study that had a dosing interval of 1 day between subjects • Added a description of the prophylactic corticosteroid regimen for Cohort 4 • Extended the Screening Period from 28 days to 35 days • Updated the basis for adjusting or tapering ammonia scavenger medication to the Investigator’s clinical judgement based on review of the totality of a subject’s clinical and laboratory data • Updated instructions for dose preparation and administration of [1-13C] sodium acetate and added a reference to the ureagenesis manual • Added instructions for subject fasting before and after administration of [1 13C]sodium acetate • Updated the timing of DMC meetings to account for additional subjects in Cohort 3 and subjects in Cohort 4 • Removed text regarding finalization of the SAP prior to the start of the study • Updated the definition of the baseline rate of ureagenesis • Updated text regarding the presentation of other laboratory results and neuropsychological tests • Updated text regarding interim analysis to allow flexibility in the timing of the interim analysis and removed text stating that any interim analyses conducted will not bias the conduct of the study

25 February 2020	• Clarified the age ranges for neonatal-onset OTC deficiency and late-onset OTC deficiency • Added guidance for monitoring ammonia levels, monitoring HAC, and modifying ammonia scavenger medication and protein-restricted diet • Added the term HAC and its definition • Updated the list of AAV8 clinical studies referenced in Section 1.2 • Removed details regarding the timing of dosing for subjects at sites in the UK, which was specific to Cohort 1 • Updated the timing of liver enzyme elevations following DTX301 administration based on study data • Added a reference to another AAV gene therapy study using a prophylactic corticosteroid regimen • Removed the definition of the baseline rate of ureagenesis • Removed "in the setting of tapering or discontinuing ammonia scavenger medications" from the exploratory endpoints for urinary orotic acid excretion and plasma glutamine and glutamate • Removed "weekly" from the exploratory endpoint for use of ammonia scavengers • Removed the exploratory endpoints for cell-mediated immune response to AAV8 and OTC • Updated the total sample size • Added text to allow abbreviated outpatient study visits to be completed by home health services where available, agreed upon by the Investigator, and allowed by local regulation • Expanded guidance for rescreening patients who fail screening • Updated text regarding the subject's plasma ammonia level prior to administration of neuropsychological tests and [1-13C]sodium acetate to include "within the range of historical ammonia levels obtained when the subject was clinically stable" • Updated text, including Inclusion Criterion 5, regarding the subject's plasma ammonia level prior to DTX301 administration to address subjects who historically maintain normal ammonia levels and subjects who historically do not have fully controlled ammonia levels with baseline management
25 February 2020	(continued) • Updated Exclusion Criterion 1 to address subjects who historically maintain normal ammonia levels, subjects who historically do not have fully controlled ammonia levels with baseline management, and subjects who have signs and symptoms of hyperammonemia during the 4-week period preceding Day 0 • Added text to allow the rate of ureagenesis assessment to be repeated during Screening if discrepant with the subject's clinical status and severity • Clarified details regarding plasma ammonia assessment prior to DTX301 administration • Added text to allow additional assessments of liver function tests, plasma ammonia, or other biomarkers at the Investigator's discretion • Added spot ammonia assessment to additional study visits • Added text to explain that subjects will be re-educated on the risks of adjusting baseline treatment on their own without guidance from the Investigator • Revised instructions for modifying baseline treatment; baseline treatment cannot be changed during or within 2 weeks of corticosteroid administration and changes to ammonia scavenger medication and protein-restricted diet cannot occur at the same time • Added text to clarify that the rate of ureagenesis cannot be used to make decisions for modifying ammonia scavenger medication or protein-restricted diet • Added guidance for reinitiating ammonia scavenger medication and reattempting modification of baseline treatment • Expanded guidance for modifying protein-restricted diet • Updated Inclusion Criterion 6 to clarify that subjects must be receiving a daily stable dose of ammonia scavenger medication • Updated the number of medical personnel required to check [1-13C] sodium acetate dosing calculations • Updated text regarding treatment compliance to include ammonia scavenger medication and protein-restricted diet • Removed the assessment of vector genome in blood • Removed the ECG assessment from the Day 1 Visit prior to DTX301 administration

25 February 2020	(continued) • Specified that, prior to initiating the prophylactic corticosteroid regimen (Cohort 4), the subject must be clinically and metabolically stable without intercurrent illness or receiving concomitant medications known to affect aminotransferase levels • Added guidance for ad hoc assessment of 24-hour plasma ammonia • Added text to specify that hospitalization due to HAC will be considered an SAE • Added text to specify that AEs will be assessed for relationship to corticosteroids in addition to the DTX301, [1-13C]sodium acetate, OTC deficiency, and hyperammonemia • Updated the CTCAE version from Version 4.03 to the most current version • Added a DMC meeting after completion of Week 12 for the first 3 subjects in Cohort 4 • Updated analysis of the rate of ureagenesis to include the relative percentage to normal healthy adults • Updated analysis of plasma ammonia to include time-normalized plasma ammonia • Decreased the frequency of viral shedding, AAV8 neutralizing antibody, and AAV8 binding antibody IgG assay assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported