Clinical trial results:
A Phase 3 Study of Lenti-D Drug Product After Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects 17 Years of Age with Cerebral Adrenoleukodystrophy (CALD)

Summary

EudraCT number	2018-001145-14
Trial protocol	GB FR DE NL IT
Global end of trial date	24 July 2023

Results information

Result version number	v1 (current)
This version publication date	09 February 2024
First version publication date	09 February 2024

Trial information

Trial identification

Sponsor protocol code	ALD-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03852498
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	bluebird bio, Inc
Sponsor organisation address	455 Grand Union Blvd, Somerville, Massachusetts, United States, 02145
Public contact	Clinical Trials Operations, Voisin Consulting, clinicaltrialinformation@voisinconsulting.com
Scientific contact	Clinical Trials Operations, Voisin Consulting, clinicaltrialinformation@voisinconsulting.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	24 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2023
Global end of trial reached?	Yes
Global end of trial date	24 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study was to evaluate the efficacy and safety of Lenti-D Drug Product after myeloablative conditioning with busulfan and fludarabine in subjects with CALD.

Protection of trial subjects:

This study was performed in accordance with Title 21, United States (US) Code of Federal Regulations (CFR) Parts 50, 54, 56 and 312 Subpart D; the International Council for Harmonisation (ICH) Guideline on Good Clinical Practice (GCP; E6); and the ethical principles outlined in the Declaration of Helsinki; and/or, where applicable, the European Directive 2001/20/EC relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use and Directive 2005/28/EC on GCP for investigational medicinal products for human use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	13 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	35
EEA total number of subjects	10

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)	33
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 8 study centers in France, Italy, Germany, the Netherlands, United Kingdom, and United States of America from 24 January 2019 to 24 July 2023.

Pre-assignment

Screening details:

A total of 35 male subjects were enrolled, underwent mobilization and infused with Lenti-D Drug Product (eli-cel).

Period 1

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

Arms

Arm title	Lenti-D Drug Product

Arm description:

On Day 1, subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to (>=) 5.0 x 10^6 CD34+ cells/kilogram (kg) (autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector encoding ABCD1 cDNA for human adrenoleukodystrophy protein, suspended in a cryopreservative solution). All subjects received myeloablative conditioning with busulfan and fludarabine over a number of days prior to drug product infusion.

Arm type	Experimental
Investigational medicinal product name	Lenti-D Drug Product
Investigational medicinal product code	
Other name	Elivaldogene autotemcel; Eli-cel; Autologous CD34+ cells transduced with Lenti -D LVV (lentiviral vector) encoding ABCD1 cDNA
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single IV infusion of Lenti-D Drug Product on Day 1.

Number of subjects in period 1	Lenti-D Drug Product
Started	35
Completed	35

Baseline characteristics

Reporting groups	
Reporting group title	Lenti-D Drug Product
Reporting group description:	
On Day 1, subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to (>=) 5.0 x 10^6 CD34+ cells/kilogram (kg) (autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector encoding ABCD1 cDNA for human adrenoleukodystrophy protein, suspended in a cryopreservative solution). All subjects received myeloablative conditioning with busulfan and fludarabine over a number of days prior to drug product infusion.	

Reporting group values	Lenti-D Drug Product	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
Age continuous			
Age at Informed Consent			
Units: years			
arithmetic mean	7		
standard deviation	± 2.1	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	35	35	
Race Units: Subjects			
White	21	21	
Black or African American	2	2	
Other	2	2	
Not Reported	10	10	
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	24	24	
Not Reported	5	5	
Unknown	1	1	

End points

End points reporting groups

Reporting group title	Lenti-D Drug Product

Reporting group description:

On Day 1, subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to (>=) 5.0 x 10^6 CD34+ cells/kilogram (kg) (autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector encoding ABCD1 cDNA for human adrenoleukodystrophy protein, suspended in a cryopreservative solution). All subjects received myeloablative conditioning with busulfan and fludarabine over a number of days prior to drug product infusion.

Primary: Percentage of Subjects Who Were Alive and Have None of the 6 Major Functional Disabilities (MFDs) at Month 24

End point title	Percentage of Subjects Who Were Alive and Have None of the 6 Major Functional Disabilities (MFDs) at Month 24[1]

End point description:

The 6 MFDs consisted of loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, complete loss of voluntary movement. Month-24 MFD-Free survival criteria defined as: alive at 24 months post infusion; have not developed any of the MFDs by 24 months post infusion; have not received rescue cell administration or allo-HSCT by 24 months post infusion; and have not withdrawn from the study or have not been lost to follow-up by 24 months post infusion. Transplant Population (TP) consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects are defined as subjects who have been followed for 24 months (i.e. Rel Day of last contact >=730) or have completed the Month 24 Visit, or discontinued from the study but would have been followed for 24 months if still on the study (i.e. Rel Day of data cut >=730), at the time of the data cut.

End point type	Primary

End point timeframe:

At Month 24

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 were performed; no inferential statistical analyses were performed.

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	85.7 (69.7 to 95.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects who Achieved Neutrophil Engraftment After Drug Product Infusion

End point title	Percentage of Subjects who Achieved Neutrophil Engraftment After Drug Product Infusion[2]

End point description:

Neutrophil engraftment is defined as achieving 3 consecutive absolute neutrophil count (ANC) laboratory values of >= 0.5x10^9 cells/liter (L) (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of eli-cel (Rel Day 43). TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects for NE if they achieved neutrophil engraftment by Rel Day 43, or had discontinued or were lost to follow-up before Rel Day 43 without achieving NE, or had been followed to at least Rel Day 43 but had not achieved NE. Subjects who discontinued or were lost to follow-up before Rel Day 43 without achieving NE were considered failures for NE.

End point type	Primary

End point timeframe:

By 42 days post-drug infusion

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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (90.0 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without Gadolinium Enhancement (i.e. GdE-) on Magnetic Resonance Imaging (MRI) at Month 24

End point title	Percentage of Subjects Without Gadolinium Enhancement (i.e. GdE-) on Magnetic Resonance Imaging (MRI) at Month 24

End point description:

Percentage of subjects without Gadolinium Enhancement (i.e. GdE-) on MRI at Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects are defined as subjects who have completed the Month 24 GdE assessment.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	94.3 (80.8 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Neurologic Function Score (NFS) From Baseline to Month 24

End point title	Number of Subjects With Change in Neurologic Function Score (NFS) From Baseline to Month 24

End point description:

NFS was a 25-point score used to evaluate the severity of gross neurologic dysfunction in CALD by scoring 15 symptoms (functional domains) across 6 categories. Listed here are the 15 symptoms followed by their maximal score out of 25 points: a) Hearing/auditory processing problems-1, b) Aphasia/apraxia-1, c) Loss of communication-3, d) Vision impairment/field cut-1, e) Cortical blindness-2, f) Swallowing/other CNS dysfunctions-2, g) Tube feeding-2, h) Running difficulties/hyperreflexia-1, i)Walking difficulties/spasticity/spastic gait (no assistance)-1, j) Spastic gait (needs assistance)-2, k) Wheelchair dependence-2, l) Complete loss of voluntary movement-3, m) Episodes of incontinence -1, n) Total incontinence-2, o) Nonfebrile seizures-1. A score of "0"= absence of clinical signs of cerebral disease. TP population. Evaluable subjects are defined as subjects who have non-missing Baseline and have completed the Month 24 NFS assessment.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Major Functional Disability (MFD)-Free Survival Rate

End point title	Major Functional Disability (MFD)-Free Survival Rate

End point description:

MFD-free survival rate was defined as percentage of subjects from drug product infusion to either second transplant, MFD, or death due to any cause, whichever occurs first. MFD-free survival rate was analyzed using Kaplan-Meier Analysis. Kaplan-Meier estimated MFD-free survival rate at 24 months after Lenti-D drug infusion was reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Deaths, MFDs, and rescue cell administration or allo-HSCT are considered events. If a subject did not experience any event, he was to be censored at the Date of Last Contact.

End point type	Secondary

End point timeframe:

At 24 months after Lenti-D drug infusion

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	88.6 (72.4 to 95.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate

End point title	Overall Survival Rate

End point description:

Overall survival rate was defined as percentage of subjects alive from date of Lenti-D drug product infusion (Day 1) to date of death of all causes. Overall survival rate was censored at the date of last visit if the subject were alive. Subjects who are alive were censored at the date of last contact. Overall survival rate was analyzed using Kaplan-Meier Analysis. TP consisted of subjects who received Lenti-D Drug Product infusion.

End point type	Secondary

End point timeframe:

At 24 months after Lenti-D drug infusion

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (100.0 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Detectable Vector Copy Number (VCN) in Peripheral Blood Cells by Month 6

End point title	Median Detectable Vector Copy Number (VCN) in Peripheral Blood Cells by Month 6

End point description:

Presence of vector sequences in the genome of cells derived from the originally transduced HSC indicates the presence of transduced cells amongst the HSC precursors. The presence of vector sequences was evaluated throughout the study in whole blood, in selected subpopulations of blood cells (including CD14+ cells), and in bone marrow when indicated. The presence of vector sequences in the genomic DNA of cells was detected using quantitative polymerase chain reaction (qPCR), and results were expressed as vector copy number (VCN; vector copies per diploid genome, c/dg). TP consisted of subjects who received Lenti-D Drug Product infusion. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Month 6 post-transplant

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: copies per diploid genome (c/dg)				
median (full range (min-max))	1.05 (0.03 to 3.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Either Acute (>= Grade 2) or Chronic Graft Versus Host Disease (GVHD) at Month 24

End point title	Percentage of Subjects Who Experienced Either Acute (>= Grade 2) or Chronic Graft Versus Host Disease (GVHD) at Month 24

End point description:

Acute GVHD graded on the Acute GVHD Grading Scale (1-4): Grade 1 is characterized as mild disease, Grade 2 as moderate, Grade 3 as severe (involvement of any organ system), and Grade 4 as life-threatening; chronic GVHD was determined by the Investigator. GVHD was seen after an eli-cel subject received a subsequent allogeneic hematopoietic stem cell transplant. No GVHD was seen in subjects who did not receive allogeneic stem cell transplants. Grade 2 nonserious GVHD was reported in a subject who received allogeneic transplant post eli-cel infusion. Percentage of subjects who experienced either acute (>= Grade 2) or chronic GVHD at Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects are defined as those who have either experienced the event by Month 24 (Rel Day 730) or have been followed for at least 12 months (Rel Day of last contact >= 365) if no events yet.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	2.9 (0.1 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Neutrophil Engraftment After Drug Product Infusion

End point title	Time to Neutrophil Engraftment After Drug Product Infusion

End point description:

Neutrophil engraftment is defined as achieving 3 consecutive absolute neutrophil count (ANC) laboratory values of >= 0.5 x 10^9 cells/liter (L) (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of eli-cel (Rel Day 43). TP consisted of subjects who received Lenti-D Drug Product infusion. Time to neutrophil engraftment after drug product infusion was reported. TP consisted of subjects who received Lenti-D Drug Product infusion

End point type	Secondary

End point timeframe:

By 42 days post-drug infusion

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Days				
median (full range (min-max))	14.0 (12 to 31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Platelet Engraftment by Month 24

End point title	Percentage of Subjects With Platelet Engraftment by Month 24

End point description:

Platelet engraftment was defined as achieving 3 consecutive unsupported platelet counts of >=20 x 10^9 cells/L (after initial post-infusion nadir) obtained on different days while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period. The first Day of 3 consecutive platelet counts >=20 x 10^9 cells/L was considered the Day of platelet engraftment. TP consisted of subjects who received Lenti-D Drug Product infusion. Subjects are evaluable for platelet engraftment if they achieved PE by Month 24, or have been followed for at least 24 months if no platelet engraftment.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (90.0 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Platelet Engraftment Post-drug Product Infusion

End point title	Time to Platelet Engraftment Post-drug Product Infusion

End point description:

Platelet Engraftment was defined as achieving 3 consecutive unsupported platelet counts of > or =20 x 10^9 cells/L (after initial post-infusion nadir) obtained on different days while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period. The first day of 3 consecutive platelet counts >=20 x 10^9 cells/L was the day of PE. Time to platelet engraftment post-drug product infusion by Month 24 was reported. TP consisted of subjects who received Lenti-D Drug Product infusion.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Days				
median (full range (min-max))	29.0 (14 to 108)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Loss of Neutrophil Engraftment Post-drug Product Infusion by Month 24

End point title	Percentage of Subjects with Loss of Neutrophil Engraftment Post-drug Product Infusion by Month 24

End point description:

Subjects were considered to have primary engraftment failure if they did not achieve NE by Relative Day 43. A subject was considered to have secondary engraftment failure if they achieved and then subsequently lost NE by the Month 24, i.e., if they met both the conditions; Achieved NE by Relative Day 43 as defined above and had sustained decline in ANC to < 0.5 x 10^9 cells/L for 3 consecutive measurements on different days after Relative Day 43, without alternate etiology. First day of the 3 consecutive ANC decline to < 0.5 x 10^9 cells/L was considered the day of secondary engraftment failure. Percentage of subjects with both primary or secondary loss of neutrophil engraftment at Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects include subjects who, had either primary engraftment failure or secondary engraftment failure by Month 24, or have been followed for at least 24 months if no events.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	0 (0.0 to 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Underwent a Subsequent Allo-Hematopoietic Stem Cell Transplantation (HSCT) Infusion by Month 24

End point title	Percentage of Subjects Who Underwent a Subsequent Allo-Hematopoietic Stem Cell Transplantation (HSCT) Infusion by Month 24

End point description:

Percentage of subjects who have undergone a subsequent allo-HSCT infusion by Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects are defined as those who received subsequent allo-HSCT, or subjects who have been followed for at least 24 months (Rel Day of last contact >= 730 or completed Month 24 visit) if no events.

End point type	Secondary

End point timeframe:

By Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	8.6 (1.8 to 23.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Experienced Transplant-related Mortality Through 100 and 365 Days Post-drug Product Infusion

End point title	Percentage of Subjects who Experienced Transplant-related Mortality Through 100 and 365 Days Post-drug Product

	Infusion

End point description:

Transplant-related mortality was determined by the investigator and summarized for the following intervals: from Rel Day 1 through 100 days post-drug product infusion (Rel Day 101) and from Rel Day 1 through 365 days post-drug product infusion (Rel Day 366). Percentage of subjects who experienced transplant-related mortality through 100 and 365 days post-drug product infusion were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects include subjects who have died from transplant-related causes by Rel Day 101 or 366 respectively or have been followed to at least Rel Day 101 or 366 respectively if no events yet.

End point type	Secondary

End point timeframe:

From time of drug product infusion through 100 and 365 days post-drug product infusion

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)				
Transplant related mortality within 100 days	0 (0.0 to 10.0)			
Transplant related mortality within 365 days	0 (0.0 to 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clinical >= Grade 3 AEs, All Investigational Medicinal Product-related AEs, all Serious Adverse Events (SAEs), and >= Grade 3 Infections

End point title	Percentage of Subjects with Clinical >= Grade 3 AEs, All Investigational Medicinal Product-related AEs, all Serious Adverse Events (SAEs), and >= Grade 3 Infections

End point description:

Adverse event was defined as any untoward medical occurrence associated with the use of a drug product in subjects, whether or not considered drug related. SAE was any AE, occurring at any dose and regardless of causality, that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or was considered an important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent an outcome listed previously. Percentage of subjects with clinical >= Grade 3 AEs, all investigational medicinal product-related AEs, all serious adverse events (SAEs), and >= Grade 3 infections were reported. Intent-to-treat (ITT) population consisted of subjects who initiated any study procedures, beginning with mobilization by granulocyte colony stimulating factor (G-CSF).

End point type	Secondary

End point timeframe:

From date of informed consent up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (not applicable)				
Subjects with at least 1 >= Grade 3 AE	100.0			
Subjects with at least 1 AE related to Eli-cel	20.0			
Subjects with at least 1 SAE	62.9			
Subjects with >= Grade 3 infections	28.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Potentially Clinically Significant Changes in Laboratory Parameters by Month 24

End point title	Percentage of Subjects With Potentially Clinically Significant Changes in Laboratory Parameters by Month 24

End point description:

Laboratory parameters included Hematology (Leukocytes [with a threshold range <4.0 x 10^9/L, >=18 x 10^9/L], Neutrophils [<1.0 x 10^9/L], Erythrocytes [<=3.0 x 10^12/L], Platelets [<=75 x 10^9/L]); Clinical chemistry (Sodium [<=126 millimoles per liter (mmol/L), >=156 mmol/L], Potassium [<=3 mmol/L, >=6 mmol/L], Glucose [<=3.0 mmol/L]), Renal (Urea Nitrogen [>=10.7 mmol/L], Creatinine [>=150 umol/L]) and liver (Alanine Aminotransferase [ALA]. Aspartate Aminotransferase [ASA], Alkaline Phosphatase [AP] with threshold range of >=3 x upper limit of normal (ULN), Bilirubin [>=34.2 micromoles per liter (umol/L)]). Clinical significance was decided by investigator. ITT population consisted of subjects who initiated any study procedures, beginning with mobilization by G-CSF.

End point type	Secondary

End point timeframe:

From Day 1 to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (not applicable)				
Hematology: Leukocytes (<4.0 x 10^9/L)	100.0			
Hematology: Leukocytes (>=18 x 10^9/L)	2.9			
Hematology: Neutrophils (<1.0 x 10^9/L)	97.1			
Hematology: Erythrocytes (<=3.0 x 10^12/L)	71.4			
Hematology: Platelets (<=75 x 10^9/L)	100.0			
Hematology: Hemoglobin (<=8.0 g/dL)	77.1			
Liver: ALA (>=3 x ULN)	11.4			
Liver: ASA (>=3 x ULN)	5.7			

Liver: AP (>=3 x ULN)	0.0			
Liver: Bilirubin (>=34.2 umol/L)	0.0			
Renal: Urea Nitrogen (>=10.7 mmol/L)	0.0			
Renal: Creatinine (>=150 umol/L)	0.0			
Chemistry: Sodium (<=126 mmol/L)	0.0			
Chemistry: Sodium (>=156 mmol/L)	0.0			
Chemistry: Potassium (<=3 mmol/L)	25.7			
Chemistry: Potassium (>=6 mmol/L)	0.0			
Chemistry: Glucose (<=3.0 mmol/L)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced >= Grade 2 Acute Graft Versus Host Disease (GVHD) by Month 24

End point title	Percentage of Subjects Who Experienced >= Grade 2 Acute Graft Versus Host Disease (GVHD) by Month 24

End point description:

Acute GVHD graded on the Acute GVHD Grading Scale (1-4): Grade 1 is characterized as mild disease, Grade 2 as moderate, Grade 3 as severe (involvement of any organ system), and Grade 4 as life-threatening; Acute GVHD was determined by the Investigator. Grade 2 nonserious GVHD was reported in a patient who received allogeneic transplant post eli-cel infusion. TP consisted of subjects who received Lenti-D Drug Product infusion. Evaluable subjects are defined as those who had >= Grade 2 acute GVHD by Month 24 (Rel Day 730), or have been followed for at least 12 months (Rel Day of last contact >= 365) if no events yet. The case of GVHD was experienced by a subject after receiving allo-HSCT.

End point type	Secondary

End point timeframe:

By Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	2.9 (0.1 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Experienced Chronic GVHD by Month 24

End point title	Percentage of Subjects who Experienced Chronic GVHD by Month 24

End point description:

Chronic GVHD graded on the Chronic GVHD Grading Scale as limited or extensive. Chronic GVHD was determined by the Investigator. Percentage of subjects who experienced chronic GVHD by Month 24 were reported. Evaluable subjects are defined as those who had chronic GVHD by Month 24 (Rel Day 730), or have been followed for at least 12 months (Rel Day of last contact >= 365) if no events yet.

End point type	Secondary

End point timeframe:

By Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of subject				
number (confidence interval 95%)	0 (0.0 to 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Emergency Room Visits (Post-Neutrophil Engraftment) By Month 24

End point title	Number of Emergency Room Visits (Post-Neutrophil Engraftment) By Month 24

End point description:

Number of emergency room visits (post-neutrophil engraftment) up to Month 24 were reported. Successful Neutrophil Engraftment Population (NEP) consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43.

End point type	Secondary

End point timeframe:

From Post-Neutrophil Engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Emergency room visits				
number (not applicable)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of In-patient Hospitalizations (Post-Neutrophil Engraftment) By Month 24

End point title	Number of In-patient Hospitalizations (Post-Neutrophil Engraftment) By Month 24

End point description:

Number of In-patient hospitalizations (post-neutrophil engraftment) by Month 24 were reported. Successful NEP consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43.

End point type	Secondary

End point timeframe:

From post-neutrophil engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Hospitalizations				
number (not applicable)	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of In-patient Hospitalizations (Post-Neutrophil Engraftment) up to Month 24

End point title	Duration of In-patient Hospitalizations (Post-Neutrophil Engraftment) up to Month 24

End point description:

Duration of in-patient hospitalizations was calculated as: Duration = (Date of hospital discharge) - (Date of hospital admission before NE) + 1. Duration of In-patient hospitalizations (post-neutrophil engraftment) up to Month 24 was reported. Successful NEP consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43. Here, "number of subjects analysed" signified those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From post-neutrophil engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Days				
median (full range (min-max))	4.0 (2 to 56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Intensive Care Units (ICU) Stays (Post-neutrophil Engraftment) By Month 24

End point title	Number of Intensive Care Units (ICU) Stays (Post-neutrophil Engraftment) By Month 24

End point description:

Number of ICU Stays (Post-neutrophil Engraftment) By Month 24 were reported. Successful NEP consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43.

End point type	Secondary

End point timeframe:

From post-neutrophil engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: ICU Stays				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of ICU Stays (Post-neutrophil Engraftment) By Month 24

End point title	Duration of ICU Stays (Post-neutrophil Engraftment) By Month 24

End point description:

Duration of ICU Stays was calculated as: Duration = (Date of hospital discharge) - (Date of hospital admission before NE) + 1. Duration of ICU Stays (Post-neutrophil Engraftment) by Month 24 was reported. Successful NEP consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43.

End point type	Secondary

End point timeframe:

From post-neutrophil engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Days				
median (full range (min-max))	(to)			

Notes:

[3] - No subjects had ICU stay and median was not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Tested Positive and Negative for Vector-Derived Replication Competent Lentivirus (RCL) Detected by Month 24

End point title	Number of Subjects who Tested Positive and Negative for Vector-Derived Replication Competent Lentivirus (RCL) Detected by Month 24

End point description:

Number of subjects who tested positive and negative for vector-derived RCL detected at Month 24 were reported. Screening of subject's blood samples for RCL at Month 24 following Lenti-D Drug infusion was performed, with the more rigorous co-culture assays used to distinguish any false positives as applicable. TP consisted of subjects who received Lenti-D Drug Product infusion. Subjects were evaluable if they have at least 1 RCL assessment

End point type	Secondary

End point timeframe:

By Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects				
Subjects tested positive for RCL	0			
Subjects tested negative for RCL	35			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Insertional Oncogenesis By Month 24

End point title	Number of Subjects With Insertional Oncogenesis By Month 24

End point description:

Insertional oncogenesis included myelodysplastic syndrome, leukemia, lymphoma. Number of subjects with insertional oncogenesis at Month 24 were reported. TP consisted of subjects who received Lenti-D

Drug Product infusion.

End point type	Secondary

End point timeframe:

By Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With >= Grade 3 Prolonged Cytopenia on or After Rel Day 60 And Rel Day 100

End point title	Number of Subjects With >= Grade 3 Prolonged Cytopenia on or After Rel Day 60 And Rel Day 100

End point description:

Number of subjects with >= Grade 3 prolonged cytopenia (i.e., decreased platelet counts, decreased neutrophil counts, and/or decreased hemoglobin counts) on or after Rel Day 60 and Rel Day 100 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion.

End point type	Secondary

End point timeframe:

Prolonged cytopenias occurring on or after Rel Day 60 and Rel Day 100 following drug product infusion

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Subjects				
On or after Rel Day 60	14			
On or after Rel Day 100	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Number of Emergency Room Visits (Post-Neutrophil Engraftment) By Month 24

End point title	Median Number of Emergency Room Visits (Post-Neutrophil Engraftment) By Month 24

End point description:

Median number of emergency room visits (post-neutrophil engraftment) up to Month 24 were reported. Successful Neutrophil Engraftment Population (NEP) consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43. Here, "number of subjects analysed" signified those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Post-Neutrophil Engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Median number of emergency room visits				
median (full range (min-max))	1.0 (1 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Number of In-patient Hospitalizations (Post-Neutrophil Engraftment) By Month 24

End point title	Median Number of In-patient Hospitalizations (Post-Neutrophil Engraftment) By Month 24

End point description:

Median number of In-patient hospitalizations (post-neutrophil engraftment) by Month 24 were reported. Successful NEP consisted of subjects who achieved neutrophil engraftment defined as having 3 consecutive ANC laboratory values of >= 0.5×10^9 cells/L (after initial post-infusion nadir) obtained on different days by Rel Day 43. Here, "number of subjects analysed" signified those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From post-neutrophil engraftment up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Median number of hospitalization				
median (full range (min-max))	1.0 (1 to 4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of informed consent up to Month 24

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Lenti-D Drug Product

Reporting group description:

On Day 1, subjects received a single IV infusion of Lenti-D Drug Product at a dose of >= 5.0 x 10^6 CD34+ cells/kg (autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector encoding ABCD1 cDNA for human adrenoleukodystrophy protein, suspended in a cryopreservative solution) following myeloablative conditioning with busulfan and fludarabine.

Serious adverse events	Lenti-D Drug Product		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 35 (62.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			

Cytogenetic abnormality			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelitis transverse			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Visual field defect			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vomiting				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Aversion				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tic				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autism spectrum disorder				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal bacteraemia				
subjects affected / exposed	2 / 35 (5.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Stenotrophomonas infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lenti-D Drug Product		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	11		
Hypotension			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	6		
Pyrexia			

subjects affected / exposed	12 / 35 (34.29%)		
occurrences (all)	20		
Catheter site pain			
subjects affected / exposed	17 / 35 (48.57%)		
occurrences (all)	24		
Gait disturbance			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hypersensitivity			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	10 / 35 (28.57%)		
occurrences (all)	17		
Hypoxia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	6		
Rhinorrhoea			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		
Tachypnoea			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	7		
Anxiety			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Enuresis			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		
Insomnia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 35 (20.00%)		
occurrences (all)	14		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	10		
Blood creatinine increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
International normalised ratio increased			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Joint injury			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	12		
Skin abrasion			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	11		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	14 / 35 (40.00%)		
occurrences (all)	18		
Speech disorder			

subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Pancytopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 29 / 35 (82.86%) 44 19 / 35 (54.29%) 21 12 / 35 (34.29%) 19 9 / 35 (25.71%) 13 29 / 35 (82.86%) 69 3 / 35 (8.57%) 3 34 / 35 (97.14%) 54		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all) Ear pain	 2 / 35 (5.71%) 2 		

subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Eye disorders			
Dry eye			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	5		
Hypermetropia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	6		
Visual impairment			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 35 (37.14%)		
occurrences (all)	21		
Abdominal pain upper			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	20 / 35 (57.14%)		
occurrences (all)	31		
Dental caries			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	9		
Gastrointestinal inflammation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	28 / 35 (80.00%)		
occurrences (all)	60		
Stomatitis			
subjects affected / exposed	34 / 35 (97.14%)		
occurrences (all)	47		
Vomiting			
subjects affected / exposed	26 / 35 (74.29%)		
occurrences (all)	60		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 35 (71.43%)		
occurrences (all)	29		
Dry skin			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	9 / 35 (25.71%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	5		
Skin exfoliation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Skin hyperpigmentation			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	9		
Skin hypopigmentation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Dermatitis contact			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Haematuria			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Urinary incontinence			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		
Cystitis noninfective			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Infections and infestations			
BK virus infection			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
COVID-19			
subjects affected / exposed	12 / 35 (34.29%)		
occurrences (all)	14		
Device related infection			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	5		
Human herpesvirus 6 infection			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Otitis media acute			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	6		
Varicella			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	7		
Pneumonia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Rhinovirus infection			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 35 (62.86%)		
occurrences (all)	29		

Fluid overload			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hypermagnesaemia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hyperphosphataemia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	11 / 35 (31.43%)		
occurrences (all)	14		
Hypomagnesaemia			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	6		
Hypophosphataemia			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	6		
Hyperkalaemia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2019	Protocol Amendment 2: • Addition of G-CSF on apheresis days to optimize cell collection • Added guidelines for administration of G-CSF after infusion of drug product to improve engraftment and align with standard study center practices • Clarified that the semi-quantitative linear amplification mediated PCR (LAMPCR) or equivalent method will be used as a screening tool for identifying integration sites (IS) of interest, but that the frequencies used to determine whether a clinical work-up is required are to be based on quantitative IS-specific methodology.
09 May 2019	Protocol Amendment 3: • Added exclusion criterion for known hypersensitivity to protamine sulfate, as there may be residual amount of protamine sulfate in eli-cel.
29 January 2020	Protocol Amendment 4: • Increased the subject number to 35, expanding the cohort in order to accrue additional efficacy and safety information. In addition, updated statistical measures in the text to reflect the change in subject number. • Revised the definition of hematological compromise in exclusion criterion #5 such that subjects are only excluded if both ANC count is < 1500 cell/mm^3 and either platelet count is < 100,000 cells/mm^3 or hemoglobin < 10g/dl. This change will allow inclusion of subjects who have only benign ethnic neutropenia and are not at risk of hematological complications. The removal of uncorrected bleeding disorder is now covered in exclusion criteria #12, as described in the list of non-substantial changes. • Revised the language around enrollment and infusion of drug product suspension criteria to allow for individualization of benefit: risk assessment. • Removed visits Month 9, Month 15, and Month 21 to decrease visit frequency to every 6 months, thereby decreasing patient burden without affecting patient safety by matching standard practice of maintenance visits every 6 months. • Removed "uncorrected bleeding disorder" from exclusion criteria #5 and added contraindicated hematological disease to exclusion criteria #12 to increase specificity and remove redundancy of each criterion. • Removed the neurological exam, NFS assessment, and MFD assessment from the Week 2 Visit to relieve patient burden in the acute post-transplantation period. • Added text in Section 6.5.10 to reflect that MRIs will also be used to determine white matter lesion progression using volumetric analysis. • Clarified in the text that mutational analysis of the ABCD1 gene is required before commencing conditioning.
11 September 2020	Protocol Amendment 5: • Revised algorithm for assessing clonal predominance. • A change to drug product release guidelines. • Clarifications around enrollment and drug product infusion suspension criteria. • Clarifications around safety endpoints and exploratory endpoints. • New guidelines around the impact of the COVID-19 pandemic, the use of antiretroviral medications, and the follow-up of newborns. • Additional non-substantial changes.

28 June 2021	Protocol Amendment 6: • Provided considerations for vaccines as concomitant medications per guidance from a regulatory agency. • In line with FDA Guidance on Long Term Follow-Up After Administration of Human Gene Therapy Product and to align protocols across regions, clarified that a sample for repeat ISA will be collected within 3 months of detection of a predominant clone. The figure was updated to indicate that ISA will be done yearly after Year 5 in Study LTF-304. • Given the severity of the disease and limited treatment options, the clinical work-up for potential malignancy has been updated to allow for a safety review to be convened rather than immediate suspension of enrollment, allowing for individual benefit:risk assessment.
22 November 2022	Protocol Amendment 8: • Protocol updated to reflect that parent study ALD-102 was completed and follow-up study LTF-304 was ongoing, where applicable. • Added reference to Skysona U.S. product package insert and IB, where applicable. • Updated exploratory endpoints relating to percent of cells expressing ALDP and VCN in cells to include both peripheral blood cells and CD14+ cells. • A new section was added to describe characterization of protocol deviations. • Impact of force of nature text updated to include war due to the impact on subject visits of the Russo-Ukrainian War. • Text was revised to increase the number/frequency of collection timepoints for CBC with differential to occur monthly during the first year after eli-cel infusion, and thereafter every 4 months until Month 24. Text also edited to note that unscheduled visits may be performed for enhanced CBC and BM abnormality monitoring. • Table row in Schedule of Events relating to bone marrow assessments updated to clarify that it included core needle biopsy and aspirate sampling and that samples were used for ISA, VCN and storage purposes. Several related footnotes were also updated. • New section added to provide more detail on sample collection for RCL Testing, Integration Site Analysis, and VCN in Blood. • Text updated to clarify that immunological studies should be conducted locally. • Updates were made to refine order of priority of sample collection and to include bone marrow collection details and prioritization. • Peripheral blood smears added to table of laboratory parameters and removed from prior section relating to performance of additional test at the Investigator’s discretion. • Clarified general statistical methods relating to analyses pertaining to subjects who undergo allo-HSCT. • A new safety analysis was added to provide the statistical definition of current oligoclonality and current persistent oligoclonality.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 October 2019	bluebird bio temporarily suspended enrollment of new subjects on 25 October 2019 following the occurrence of delayed hematopoietic reconstitution in 2 subjects treated with eli-cel. On 30 January 2020 the decision was made to re-open enrollment.	30 January 2020

Notes:

Limitations and caveats

None reported