



## Clinical trial results:

### A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced with Lenti D Lentiviral Vector for the Treatment of Cerebral Adrenoleukodystrophy (CALD)

#### Summary

EudraCT number	2011-001953-10
Trial protocol	GB FR DE Outside EU/EEA
Global end of trial date	26 March 2021

#### Results information

Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

#### Trial information

##### Trial identification

Sponsor protocol code	ALD-102
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01896102
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	bluebird bio, Inc
Sponsor organisation address	60 Binney Street, Cambridge, Massachusetts, United States, 02142
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001244-PIP01-11
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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2021
Global end of trial reached?	Yes
Global end of trial date	26 March 2021
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 (elicel) 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	21 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	32
EEA total number of subjects	2

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	31
Adolescents (12-17 years)	1
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 in France, Germany, the United Kingdom and the United States from 21 August 2013 (First subject signed informed consent) to 26 March 2021 (Last subject last visit).

### Pre-assignment

Screening details:

A total of 32 subjects were enrolled and treated in this study. All male subjects with CALD were treated 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
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Arm description:

Subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to ( $\geq$ )  $5.0 \times 10^6$  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) on Day 0.

Arm type	Experimental
Investigational medicinal product name	Lenti-D Drug Product
Investigational medicinal product code	
Other name	Autologous CD34+ cells transduced with Lenti -D LVV (lentiviral vector) encoding ABCD1 cDNA, elivaldogene autotemcel, eli-cel
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 0.

Number of subjects in period 1	Lenti-D Drug Product
Started	32
Completed	29
Not completed	3
Death	1
Subject to receive allogeneic transplant	2

## Baseline characteristics

### Reporting groups

Reporting group title	Lenti-D Drug Product
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Reporting group description:

Subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to ( $\geq$ )  $5.0 \times 10^6$  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) on Day 0.

Reporting group values	Lenti-D Drug Product	Total	
Number of subjects	32	32	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	6		
standard deviation	$\pm 2.4$	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	32	32	
Race			
Units: Subjects			
White	15	15	
Black Or African American	1	1	
Native Hawaiian or Pacific Islander	0	0	
Asian	1	1	
American Indian or Alaska Native	0	0	
Other	5	5	
Not Reported	10	10	
Ethnicity			
Units: Subjects			
Hispanic	12	12	
Non-Hispanic	17	17	
Not Reported	3	3	

## End points

### End points reporting groups

Reporting group title	Lenti-D Drug Product
Reporting group description:	
Subjects received a single intravenous (IV) infusion of Lenti-D Drug Product at a dose of greater than or equal to ( $\geq$ ) $5.0 \times 10^6$ 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) on Day 0.	

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

End point title	Proportion of Subjects Who are Alive and Have None of the 6 Major Functional Disabilities (MFDs) at Month 24 <sup>[1]</sup>
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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 was 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. The proportion of subjects was calculated by dividing that subjects who are alive by the number of evaluable subjects and multiplying by 100%.

End point type	Primary
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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.

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	90.6 (75.0 to 98.0)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of Subjects Who Experienced Either Acute ( $\geq$ Grade II) or Chronic Graft Versus Host Disease (GVHD) at Month 24

End point title	Proportion of Subjects Who Experienced Either Acute ( $\geq$ Grade II) or Chronic Graft Versus Host Disease (GVHD) at Month 24 <sup>[2]</sup>
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End point description:

Proportion of subjects who experienced with either acute ( $\geq$  Grade II) or chronic GVHD at Month 24 was reported. Acute GVHD graded on the Acute GVHD Grading Scale (I-IV): Grade I is characterized as

mild disease, Grade II as moderate, Grade III as severe (involvement of any organ system), and Grade IV as life-threatening; chronic GVHD was determined by the Investigator. TP consisted of subjects who received Lenti-D Drug Product infusion. The proportion of subjects was calculated by dividing that subjects who experienced with either acute ( $\geq$  Grade II) or chronic GVHD by the number of evaluable subjects and multiplying by 100%.

End point type	Primary
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End point timeframe:

At Month 24

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.

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	0.0 (0.0 to 10.9)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Who Demonstrated Resolution of Gadolinium Positivity on MRI at Month 24

End point title	Proportion of Subjects Who Demonstrated Resolution of Gadolinium Positivity on MRI at Month 24
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End point description:

Proportion of subjects who demonstrated resolution of gadolinium positivity (i.e., GdE-) on Magnetic Resonance Imaging (MRI) at Month 24 were reported. 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. The proportion of subjects was calculated by dividing that subjects who demonstrated resolution of gadolinium positivity by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Percentage of Subjects				
number (confidence interval 95%)	86.7 (69.3 to 96.2)			

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Time to Sustained Resolution of Gadolinium Positivity on MRI up to Month 24**

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End point title	Time to Sustained Resolution of Gadolinium Positivity on MRI up to Month 24
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End point description:

Sustained resolution of gadolinium positivity was defined as having at least two consecutive GdE- results by MRI without a subsequent evaluation indicating GdE+. 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
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End point timeframe:

Up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Days				
median (full range (min-max))	77.0 (25 to 551)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of Subjects With Change in Total Neurologic Function Score (NFS) from Baseline up to Month 24**

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End point title	Number of Subjects With Change in Total Neurologic Function Score (NFS) from Baseline up to Month 24
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End point description:

NFS was a 25-point composite scale used to evaluate the severity of gross neurologic dysfunction in CALD by scoring 15 symptoms across 6 categories: Hearing/auditory processing problems-1; Aphasia/apraxia-1; Loss of communication-3; Vision impairment/field cut-1; Cortical blindness-2; Swallowing/other central nervous system dysfunctions-2; Tube feeding-2; Running difficulties/hyperreflexia-1; Walking difficulties/spasticity/spastic gait (no assistance)-1; Spastic gait (needs assistance)-2; Wheelchair dependence-2; Complete loss of voluntary movement-3; Episodes of incontinence -1; Total incontinence-2; Nonfebrile seizures-1. A score of "0" denotes absence of clinical signs of cerebral disease. TP analysis set was used. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to Month 24



<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Subjects				
Decreased	0			
No change	26			
Increased <=3	3			
Increased >3	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Major Functional Disability (MFD)-free Survival Rate at 24 Months

End point title	Major Functional Disability (MFD)-free Survival Rate at 24 Months
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 analysed using Kaplan-Meier Analysis. Kaplan-Meier estimated MFD-free survival rate at 24 months after eli-cel infusion was reported. TP consisted of subjects who received Lenti-D Drug Product infusion.	
End point type	Secondary
End point timeframe:	
At 24 months after eli-cel infusion	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of subjects				
number (confidence interval 95%)	90.6 (73.7 to 96.9)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival Rate at 24 Months

End point title	Overall Survival Rate at 24 Months
End point description:	
Overall survival rate was defined as percentage of subjects from date of Lenti-D drug product infusion (Day 0) to date of death of all causes. Overall survival rate was censored at the date of last visit if the subject was still alive. Subjects who are alive were censored at the date of last contact. Overall survival rate was analysed using Kaplan-Meier Analysis. Kaplan-Meier estimated overall survival rate at 24 months after eli-cel infusion was reported. TP consisted of subjects who received Lenti-D Drug Product infusion. Percentage of subjects who survived till Month 24 were reported.	

End point type	Secondary
End point timeframe:	
At 24 months after eli-cel infusion	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of subjects				
number (confidence interval 95%)	96.7 (78.6 to 99.5)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Neutrophil Engraftment at 42 Days Post-drug Product Infusion

End point title	Proportion of Subjects With Neutrophil Engraftment at 42 Days Post-drug Product Infusion
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End point description:

Neutrophil engraftment (NE) was defined as achieving 3 consecutive absolute neutrophil count (ANC) laboratory values of  $\geq 0.5 \times 10^9$  cells/Liter (L) (after initial post-infusion nadir) obtained on different days at 42 days post-infusion of Lenti-D Drug Product (Relative Day 43). Proportion of subjects with neutrophil engraftment at 42 Days post-drug product infusion were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. The proportion of subjects was calculated by dividing that subjects with neutrophil engraftment by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At 42 days post-drug infusion

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	100.0 (89.1 to 100.0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Neutrophil Engraftment Post-drug Product Infusion

End point title	Time to Neutrophil Engraftment Post-drug Product Infusion
End point description:	
Neutrophil engraftment was defined as achieving 3 consecutive ANC laboratory values of $\geq 0.5 \times 10^9$ cells/L (after initial post-infusion nadir) obtained on different days by 42 days post-infusion of Lenti-D Drug Product (Relative Day 43). TP consisted of subjects who received Lenti-D Drug Product infusion.	
End point type	Secondary
End point timeframe:	
At 42 days post-drug infusion	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Days				
median (full range (min-max))	13.0 (11 to 41)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Platelet Engraftment at Month 24

End point title	Proportion of Subjects With Platelet Engraftment at Month 24
End point description:	
Platelet engraftment was defined as achieving 3 consecutive unsupported platelet counts of $\geq 20 \times 10^9$ 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 $\geq 20 \times 10^9$ cells/L was the day of PE. Proportion of subjects with platelet engraftment at Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion. The proportion of subjects was calculated by dividing that subjects with platelet engraftment by the number of evaluable subjects and multiplying by 100%.	
End point type	Secondary
End point timeframe:	
At Month 24	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	100 (89.1 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
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End point description:

Platelet engraftment was defined as achieving 3 consecutive unsupported platelet counts of  $\geq 20 \times 10^9$  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  $\geq 20 \times 10^9$  cells/L was the day of PE. Time to platelet engraftment post-drug product infusion up to Month 24 was reported. TP consisted of subjects who received Lenti-D Drug Product infusion.

End point type	Secondary
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End point timeframe:

Up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Days				
median (full range (min-max))	32.0 (16 to 60)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Engraftment failure at Month 24

End point title	Proportion of Subjects With Engraftment failure at Month 24
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End point description:

Subject was considered to have primary engraftment failure if he did not achieve NE by Relative Day 43. A subject was considered to have secondary engraftment failure if he achieved and then subsequently lost NE by the Month 24, i.e., if he met both the conditions:- Achieved NE by Relative Day 43 as defined above;- Had sustained decline in ANC to  $< 0.5 \times 10^9$  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  $< 0.5 \times 10^9$  cells/L was considered the day of secondary engraftment failure. Proportion of subjects with primary or secondary engraftment failure at Month 24 were reported. TP population. Number of subjects analysed signifies those subjects who were evaluable for this endpoint. The proportion of subjects was calculated by dividing that subjects with engraftment failure by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percentage of Subjects				
number (confidence interval 95%)	0.0 (0.0 to 11.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects Who Undergone a Subsequent Hematopoietic Stem Cell (HSC) Infusion at Month 24

End point title	Proportion of Subjects Who Undergone a Subsequent Hematopoietic Stem Cell (HSC) Infusion at Month 24
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End point description:

Proportion of subjects who undergone a HSC infusion at Month 24 were reported. 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. The proportion of subjects was calculated by dividing that subjects who undergone a HSC infusion by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of Subjects				
number (confidence interval 95%)	6.5 (0.8 to 21.4)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Transplant-related Mortality Through 100 and 365 Days Post-drug Product Infusion

End point title	Proportion of Subjects With Transplant-related Mortality Through 100 and 365 Days Post-drug Product Infusion
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End point description:

Transplant-related mortality was determined by the Investigator. Proportion of subjects with 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. The proportion of subjects was calculated by dividing that subjects with transplant-related mortality by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
End point timeframe:	
From time of drug product infusion through 100 and 365 days post-drug product infusion	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)				
Transplant-related mortality within 100 days	0.0 (0.0 to 10.9)			
Transplant-related mortality within 365 days	0.0 (0.0 to 10.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Adverse Events (AEs), Serious AEs, Grade $\geq 3$ AE, Related AEs, Related SAEs and Related Grade $\geq 3$ AEs

End point title	Proportion of Subjects With Adverse Events (AEs), Serious AEs, Grade $\geq 3$ AE, Related AEs, Related SAEs and Related Grade $\geq 3$ AEs
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End point description:

AE: any untoward medical occurrence associated with the use of a drug 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. Proportion of subjects with all AEs, all SAEs, all drug-product related AEs, clinical AEs  $\geq$  Grade 3 AEs, AEs  $\geq$  Grade 3 infections were reported. Intent-to-treat (ITT) population: subjects who initiated any study procedures, beginning with mobilization by G-CSF. Proportion of subjects was calculated by dividing that subjects with AEs by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
End point timeframe:	
From date of informed consent up to Month 24	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (not applicable)				
Subjects: at least 1 AE	100.0			
Subjects: at least 1 SAE	65.6			
Subjects: at least 1 AE related to Eli-cel	9.4			

Subjects: at least 1 SAE related to Eli-cel	3.1			
Subjects: at least 1 Grade $\geq 3$ AE	93.8			
Subjects: at least 1 Grade $\geq 3$ AE related to Eli-cel	3.1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects With Potentially Clinical Significant Changes in Laboratory Parameters up to Month 24

End point title	Proportion of Subjects With Potentially Clinical Significant Changes in Laboratory Parameters up to Month 24
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End point description:

Laboratory parameters included hematology (Leukocytes [with a threshold (TS) range  $<4.0 \times 10^9/L$ ,  $\geq 18 \times 10^9/L$ ], Neutrophils [ $<1.0 \times 10^9/L$ ], Erythrocytes [ $\leq 3.0 \times 10^{12}/L$ ], Platelets [ $\leq 75 \times 10^9/L$ ]); clinical chemistry (Sodium [ $\leq 126$  millimoles per liter (mmol/L),  $\geq 156$  mmol/L], Potassium [ $\leq 3$  mmol/L,  $\geq 6$  mmol/L], Glucose [ $\leq 3.0$  mmol/L], Urea Nitrogen [ $\geq 10.7$  mmol/L], Creatinine [ $\geq 150$   $\mu\text{mol/L}$ ]) and liver function tests (LFT) (Alanine Aminotransferase [ALA], Aspartate Aminotransferase [ASA], Alkaline Phosphatase [AP] with TS range of  $\geq 3 \times$  upper limit of normal (ULN), Bilirubin [ $\geq 34.2$  micromoles per liter ( $\mu\text{mol/L}$ )). Clinical significance was decided by investigator. ITT population consisted of subjects who initiated any study procedures, beginning with mobilization by G-CSF. Proportion of subjects was calculated by dividing that subjects with potentially clinical significant changes in laboratory parameters by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

From time of drug product infusion up to Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (not applicable)				
Hematology: Leukocytes ( $<4.0 \times 10^9/L$ )	100.0			
Hematology: Leukocytes ( $\geq 18 \times 10^9/L$ )	0.0			
Hematology: Neutrophils ( $<1.0 \times 10^9/L$ )	78.1			
Hematology: Erythrocytes ( $\leq 3.0 \times 10^{12}/L$ )	43.8			
Hematology: Platelets ( $\leq 75 \times 10^9/L$ )	96.9			
Chemistry: Sodium ( $\leq 126$ mmol/L)	0.0			
Chemistry: Sodium ( $\geq 156$ mmol/L)	0.0			
Chemistry: Potassium ( $\leq 3$ mmol/L)	21.9			
Chemistry: Potassium ( $\geq 6$ mmol/L)	0.0			
Chemistry: Glucose ( $\leq 3.0$ mmol/L)	0.0			
Chemistry: Urea Nitrogen ( $\geq 10.7$ mmol/L)	0.0			
Chemistry: Creatinine ( $\geq 150$ $\mu\text{mol/L}$ )	0.0			

LFT: ALA ( $\geq 3 \times \text{ULN}$ )	3.1			
LFT: ASA ( $\geq 3 \times \text{ULN}$ )	3.1			
LFT: AP ( $\geq 3 \times \text{ULN}$ )	0.0			
LFT: Bilirubin ( $\geq 34.2 \text{ umol/L}$ )	0.0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With $\geq$ Grade II Acute GVHD at Month 24

End point title	Proportion of Subjects With $\geq$ Grade II Acute GVHD at Month 24
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End point description:

Proportion of subjects with  $\geq$  Grade II acute GVHD at Month 24 were reported. Acute GVHD graded on the Acute GVHD Grading Scale (I-IV): Grade I is characterized as mild disease, Grade II as moderate, Grade III as severe (involvement of any organ system), and Grade IV as life-threatening. TP consisted of subjects who received Lenti-D Drug Product infusion. The proportion of subjects was calculated by dividing that subjects with  $\geq$  Grade II acute GVHD by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At Month 24

End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	0.0 (0.0 to 10.9)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects With Chronic GVHD at Month 24

End point title	Proportion of Subjects With Chronic GVHD at Month 24
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End point description:

Proportion of subjects with chronic GVHD at Month 24 were reported. Chronic GVHD was determined by the Investigator. TP consisted of subjects who received Lenti-D Drug Product infusion. The proportion of subjects was calculated by dividing that subjects with chronic GVHD by the number of evaluable subjects and multiplying by 100%.

End point type	Secondary
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End point timeframe:

At Month 24



End point values	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of Subjects				
number (confidence interval 95%)	0.0 (0.0 to 10.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Emergency Room Visits (Post-Neutrophil Engraftment) up to Month 24

End point title	Number of Emergency Room Visits (Post-Neutrophil Engraftment) up to Month 24
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End point description:

Number of emergency room visits (post-neutrophil engraftment) up to Month 24 were reported. The successful Neutrophil Engraftment Population (NEP) consisted of subjects who achieved NE defined as having 3 consecutive ANC laboratory values of  $\geq 0.5 \times 10^9$  cells/L (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of Lenti-D Drug Product.

End point type	Secondary
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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	32			
Units: Emergency room visits				
number (not applicable)	13			

### Statistical analyses

No statistical analyses for this end point

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

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

Number of In-patient hospitalizations (post-neutrophil engraftment) up to Month 24 were reported. The

successful NEP consisted of subjects who achieved NE defined as having 3 consecutive ANC laboratory values of  $\geq 0.5 \times 10^9$  cells/L (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of Lenti-D Drug Product.

End point type	Secondary
End point timeframe:	
From post-neutrophil engraftment up to Month 24	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Hospitalizations				
number (not applicable)	14			

### 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
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End point description:

Duration of In-patient hospitalizations (post-neutrophil engraftment) up to Month 24 was reported. The successful NEP consisted of subjects who achieved NE defined as having 3 consecutive ANC laboratory values of  $\geq 0.5 \times 10^9$  cells/L (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of Lenti-D Drug Product. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
From post-neutrophil engraftment up to Month 24	

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Days				
median (full range (min-max))	3.0 (2 to 33)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Intensive Care Units (ICU) Stays (Post-neutrophil

**Engraftment) up to Month 24**

End point title	Number of Intensive Care Units (ICU) Stays (Post-neutrophil Engraftment) up to Month 24
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End point description:

Number of ICU Stays (Post-neutrophil Engraftment) up to Month 24 were reported. The successful NEP consisted of subjects who achieved NE defined as having 3 consecutive ANC laboratory values of  $\geq 0.5 \times 10^9$  cells/L (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of Lenti-D Drug Product.

End point type	Secondary
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End point timeframe:

From post-neutrophil engraftment up to Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: ICU Stays				
number (not applicable)	1			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of ICU Stays (Post-neutrophil Engraftment) up to Month 24**

End point title	Duration of ICU Stays (Post-neutrophil Engraftment) up to Month 24
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End point description:

Duration of ICU Stays (Post-neutrophil Engraftment) up to Month 24 was reported. The successful NEP consisted of subjects who achieved NE defined as having 3 consecutive ANC laboratory values of  $\geq 0.5 \times 10^9$  cells/L (after initial post-infusion nadir) obtained on different days by 42 days postinfusion of Lenti-D Drug Product. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

From post-neutrophil engraftment up to Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Days				
median (full range (min-max))	12.0 (12 to 12)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Vector-derived Replication Competent Lentivirus (RCL) Detected at Month 24

End point title	Number of Subjects With Vector-derived Replication Competent Lentivirus (RCL) Detected at Month 24
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End point description:

Number of subjects with Vector-derived RCL detected at Month 24 were reported. TP consisted of subjects who received Lenti-D Drug Product infusion.

End point type	Secondary
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End point timeframe:

At Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Subjects	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Insertional Oncogenesis at Month 24

End point title	Number of Subjects With Insertional Oncogenesis at Month 24
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End point description:

Insertional oncogenesis included myelodysplasia, leukemia, lymphoma malignancies. 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
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End point timeframe:

At Month 24

<b>End point values</b>	Lenti-D Drug Product			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Subjects	0			

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of informed consent up to Month 24

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Lenti-D Drug Product
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Reporting group description:

Subjects received a single IV infusion of Lenti-D Drug Product at a dose of  $\geq 5.0 \times 10^6$  CD34+ cells/kg (autologous CD34+ cell-enriched population that contains cells transduced with Lenti-D lentiviral vector encoding human adrenoleukodystrophy protein, suspended in a cryopreservative solution) on Day 0.

Serious adverse events	Lenti-D Drug Product		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 32 (65.63%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 32 (3.13%)		
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	8 / 32 (25.00%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Vascular device infection			



subjects affected / exposed	3 / 32 (9.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cystitis viral			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 32 (3.13%)		
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 %

<b>Non-serious adverse events</b>	Lenti-D Drug Product		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 32 (34.38%)		
occurrences (all)	11		
Catheter site pain			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	8		
Catheter site haemorrhage			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Psychiatric disorders			
Enuresis			

subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Agitation			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Encopresis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	8		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Blood creatinine increased			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
International normalised ratio increased			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Protein total decreased			

subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	7 / 32 (21.88%)		
occurrences (all)	7		
Allergic transfusion reaction			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Fall			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Sinus bradycardia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Tachycardia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 32 (40.63%)		
occurrences (all)	13		
Dizziness			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Dystonia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Lethargy			

subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Sensory loss subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Speech disorder subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Visual field defect subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
<b>Blood and lymphatic system disorders</b> Anaemia subjects affected / exposed occurrences (all)	31 / 32 (96.88%) 31		
Thrombocytopenia subjects affected / exposed occurrences (all)	31 / 32 (96.88%) 31		
Neutropenia subjects affected / exposed occurrences (all)	30 / 32 (93.75%) 30		
Febrile neutropenia subjects affected / exposed occurrences (all)	20 / 32 (62.50%) 20		
Leukopenia subjects affected / exposed occurrences (all)	11 / 32 (34.38%) 11		
Lymphopenia subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 6		
<b>Gastrointestinal disorders</b> Nausea subjects affected / exposed occurrences (all)	30 / 32 (93.75%) 30		
Vomiting			

subjects affected / exposed	28 / 32 (87.50%)		
occurrences (all)	28		
Stomatitis			
subjects affected / exposed	27 / 32 (84.38%)		
occurrences (all)	27		
Abdominal pain			
subjects affected / exposed	17 / 32 (53.13%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	14 / 32 (43.75%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	9 / 32 (28.13%)		
occurrences (all)	9		
Oral pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Proctitis			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	23 / 32 (71.88%)		
occurrences (all)	23		
Pruritus			
subjects affected / exposed	7 / 32 (21.88%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Skin hyperpigmentation			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		

Rash maculo-papular subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3		
Dermatitis diaper subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Bone pain subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Infections and infestations Vascular device infection subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3		
Enterobiasis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Rhinovirus infection subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Viral infection subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 32 (68.75%)		
occurrences (all)	22		
Hypokalaemia			
subjects affected / exposed	20 / 32 (62.50%)		
occurrences (all)	20		
Hypomagnesaemia			
subjects affected / exposed	9 / 32 (28.13%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		
Fluid retention			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Iron deficiency			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2013	Protocol Amendment 2: - Original protocol to enroll subjects.
19 June 2013	Protocol Amendment 3: - Changed inclusion criteria from boys $\leq 15$ years of age to boys $\leq 17$ years of age. - Loosened the exclusion criteria from [12 months before D-60 to 3 months before D-60] of receiving an investigational study drug or procedure. - Subjects who experience engraftment failure changed from being terminated from the study to continue to be followed for safety and efficacy after engraftment failure. - Added discontinuation criteria: * Vector copy number (VCN) is undetectable ( $< 0.002$ copies per cell) * neurological decline between Screening and Day -11, as evidence by NFS $> 1$ or Loes Score $> 9$ - Added plerixafor as a potential mobilizing agent if filgrastim alone is not sufficient. - Reduced the number of rounds of apheresis (5 to 3) per mobilization cycle. - Removed 6 neuropsychological tests that are not universally performed; added 4 neuropsychological tests that are more suitable for a global, multicenter study.
04 October 2013	Protocol Amendment 4: - Removed requirement of a positive replication competent lentivirus reverse transcriptase-polymerase chain reaction (RCL RT-PCR) test before p24 protein enzyme-linked immunosorbent assay (ELISA) testing.
09 July 2014	Protocol Amendment 5.1: - To align with current standards, changed VCN discontinuation criterion from $< 0.002$ to $< 0.0003$ copies per cell. - Clarified that enrollment will be temporarily held if any death occurs on the study. - To align with current standards, changed criterion of work-up for clonal dominance from greater than ( $>$ ) 20 percent (%) of cells to $> 10\%$ of total PBLs with gene marking derived from a single clone. - Removed very long-chain fatty acids (VLCFA) testing at Month 3 Visit to allow time for engrafted cells to promote metabolism of VLCFA. - Clarify that filgrastim may be used at the Investigator's discretion after infusion of eli-cel. - Clarified that Grade 3 and Grade 4 lab values related to myeloablative conditioning will not be reported as an SAE unless they meet the requirement of being immediately life threatening.
04 June 2016	Protocol Amendment 6.2: - Increased the number of subjects to be infused with drug product from 15 to 17. - Allowed for the use of lenograstim in addition to filgrastim for G-CSF use during mobilization. - Added collection and analysis of GVHD (GVHD not expected in ALD 102 but important in comparing eli-cel with allo-HSCT). - Removed integration site analysis (ISA) from Month 3 Visit; Added ISA back into Month 18. - Month 24 Visit window changed from $\pm 60$ days to $\pm 30$ days to align with previous visit windows.

01 November 2016	<p>Protocol Amendment 7:</p> <ul style="list-style-type: none"> <li>- Increased the number of subjects to be infused with drug product from 17 to 25.</li> <li>- Added assessments to Screening, Month 12, and Month 24 visits to confirm reconstitution of immune system post-drug product infusion.</li> <li>- Specified that discontinuation due to disease progression or an SAE related to drug product, or who develop an MFD or die prior to Month 24 will be considered treatment failures in the primary efficacy analysis.</li> <li>- Added that subjects who are evaluated after Month 24 and are MFD free will be considered successful in primary analysis.</li> <li>- Expanded comparison population for safety endpoints to include allo HSCT-treated population in Study ALD-103.</li> </ul>
06 October 2017	<p>Protocol Amendment 8:</p> <ul style="list-style-type: none"> <li>- Increased the number of subjects to be infused with drug product from 25 to approximately 30.</li> <li>- Clarified that the assessment of MFDs does not require an NFS assessment .</li> <li>- Clarified secondary efficacy endpoint for time to sustained resolution of gadolinium positivity on MRI, where sustained is defined as resolution without a subsequent evaluation indicating gadolinium positivity.</li> <li>- Increased the dose for the eli-cel to <math>\geq 5.0 \times 10^6</math> CD34+ cells/kg based on data from first 21 patients showing that doses of <math>\geq 6 \times 10^6</math> were well tolerated.</li> <li>- Increased the target cell collection during apheresis to <math>12 \times 10^6</math> CD34+ cells/kg.</li> <li>- Increased volume range to between 20 and 80 milliliter (mL) for infusion to allow for infusion of two drug product lots of 2 bags each.</li> <li>- Based on regulatory recommendations, adjusted guideline on blood sample volume limits to not exceed 3% of total blood volume during a period of four weeks and to not exceed 1% at any single time.</li> <li>- Added possibility to screen for human immunodeficiency virus-1 (HIV-1) if the replication competent lentivirus (RCL) screening assay has a positive result.</li> <li>- Added that additional analyses can be performed for regulatory purposes any time after the first 17 subjects complete the study.</li> <li>- Clarified that occurrence of a second transplant is considered a treatment failure.</li> <li>- Adjusted point estimates based on the number of subjects planned for enrollment.</li> <li>- Indicated that the all transplant population of ALD-101 and ALD-103 would be used for safety endpoints as a more appropriate comparator.</li> </ul>
24 August 2018	<p>Protocol Amendment 9:</p> <ul style="list-style-type: none"> <li>- Changed "incidence" to "proportion of subjects" in several endpoints, which is considered more accurate from a statistical standpoint. This change in terminology does not change the interpretation or analyses of the concerned endpoints.</li> <li>- Clarified definitions for neutrophil engraftment, neutrophil engraftment failure, platelet engraftment, and platelet engraftment failure.</li> <li>- Immunological Testing was added to Month 3 and Month 6 Visits to allow assessment of the rapidity of immune reconstitution after transplant.</li> <li>- Added that the primary efficacy endpoint will also be analyzed for the ITT population if it is different than the TP, in response to Regulatory Agencies' recommendation during scientific advice.</li> <li>- Updated the Baseline definitions for safety and efficacy analyses to reflect most recent value not impacted by a study procedure.</li> </ul>

23 September 2020	<p>Protocol Amendment 10:</p> <ul style="list-style-type: none"> <li>- Separated the safety endpoint for insertional oncogenesis and clonal predominance into two endpoints, with insertional oncogenesis as a secondary endpoint and clonal predominance as an exploratory endpoint.</li> <li>- Revised exploratory efficacy endpoints to provide individual outputs rather than change over time, as absolute values are a more informative parameter for analysis.</li> <li>- Added text to provide guidelines around study procedures and assessments impacted by the COVID-19 pandemic.</li> <li>- Added text to indicate that clinical work-up for unexpected blood test results may be performed.</li> <li>- Updated the assessment of clonal predominance to be based on frequency of clones with lentiviral vector (LVV) insertions rather than on frequency of individual LVV insertion sites.</li> </ul>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 June 2016	There was an approximately 22 month interruption in enrollment between infusion of the last subject in the initial cohort and enrollment of the next subject in the overall cohort.	06 February 2017

Notes:

## Limitations and caveats

None reported