



## Clinical trial results:

### Phase 2, Randomized, Double-Blind, Placebo Controlled, Nested Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ARCT-810 in Adolescent and Adult Participants with Ornithine Transcarbamylase Deficiency

#### Summary

EudraCT number	2021-001081-38
Trial protocol	BE ES FR SE IT
Global end of trial date	31 October 2024

#### Results information

Result version number	v1 (current)
This version publication date	23 November 2025
First version publication date	23 November 2025

#### Trial information

##### Trial identification

Sponsor protocol code	ARCT-810-03
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05526066
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Arcturus Therapeutics, Inc.
Sponsor organisation address	10628 Science Center Dr #250, San Diego, United States, 92121
Public contact	Arcturus Therapeutics, Inc., Arcturus Therapeutics, Inc., 858 900-2660, clinicaltrials@arcturusrx.com
Scientific contact	Arcturus Therapeutics, Inc., Arcturus Therapeutics, Inc., 858 900-2660, clinicaltrials@arcturusrx.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?	Yes

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	08 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2024
Global end of trial reached?	Yes
Global end of trial date	31 October 2024
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

Main objective of the trial:

To assess safety and tolerability of ARCT-810 in adult and adolescent ( $\geq 12$  years) participants with ornithine transcarbamylase (OTC) deficiency.

Protection of trial subjects:

This study was run according to the principles of the International Council for Harmonization (ICH) harmonized tripartite guideline E6(R2): Good Clinical Practices (GCP). The investigator performed all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the protocol, and all national, state, and local laws or regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	8
EEA total number of subjects	6

Notes:

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**Subjects enrolled per age group**

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	4
Adults (18-64 years)	4

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was planned with two ascending dose cohorts (Cohort A and Cohort B). The study was terminated based on the sponsor's decision around enrollment rate prior to initiating Cohort B.

### Pre-assignment

Screening details:

The study comprised at least a 28-day (4-week) Screening and Diet Run-in (Stabilization) Period running concurrently.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ARCT-810

Arm description:

On Day 1, participants received a single dose of ARCT-810 via intravenous infusion. Participants then received a further 5 doses of ARCT-810 on Days 15, 29, 43, 57 and 71.

Arm type	Experimental
Investigational medicinal product name	ARCT-810
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As specified in the arm description.

<b>Arm title</b>	Placebo
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Arm description:

On Day 1, participants received a single dose of placebo via intravenous infusion. Participants then received a further 5 doses of placebo on Days 15, 29, 43, 57 and 71.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As specified in the arm description.

<b>Number of subjects in period 1</b>	ARCT-810	Placebo
Started	6	2
Received at Least 1 Dose	6	2
Completed	5	2
Not completed	1	0
Adverse event, non-fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	ARCT-810
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Reporting group description:

On Day 1, participants received a single dose of ARCT-810 via intravenous infusion. Participants then received a further 5 doses of ARCT-810 on Days 15, 29, 43, 57 and 71.

Reporting group title	Placebo
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Reporting group description:

On Day 1, participants received a single dose of placebo via intravenous infusion. Participants then received a further 5 doses of placebo on Days 15, 29, 43, 57 and 71.

Reporting group values	ARCT-810	Placebo	Total
Number of subjects	6	2	8
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	3	1	4
Adults (18-64 years)	3	1	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	19.7	18.5	
standard deviation	± 4.97	± 3.54	-
Gender Categorical			
Units: Subjects			
Female	2	2	4
Male	4	0	4
Race			
Units: Subjects			
White	5	1	6
Other	1	1	2

## End points

### End points reporting groups

Reporting group title	ARCT-810
Reporting group description:	
On Day 1, participants received a single dose of ARCT-810 via intravenous infusion. Participants then received a further 5 doses of ARCT-810 on Days 15, 29, 43, 57 and 71.	
Reporting group title	Placebo
Reporting group description:	
On Day 1, participants received a single dose of placebo via intravenous infusion. Participants then received a further 5 doses of placebo on Days 15, 29, 43, 57 and 71.	

### Primary: Number of Participants with Adverse Events (AEs) and Treatment-related AEs

End point title	Number of Participants with Adverse Events (AEs) and Treatment-related AEs <sup>[1]</sup>
End point description:	
An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE was considered related to the medicinal (investigational) product. A treatment-related AE was defined as an AE that was considered related to the medicinal (investigational) product by the investigator. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module. Measured in the safety population, which included all participants who were randomized and received any study drug.	
End point type	Primary
End point timeframe:	
Up to approximately 28 weeks	

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: No statistical analyses were planned for this endpoint.

End point values	ARCT-810	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: Participants				
AEs	6	2		
Treatment-related AEs	5	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration Versus Time Curve (AUC) from Time Zero to the Last Quantifiable Time Point (AUClast) of ARCT-810 mRNA and Lipid Components

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC) from Time Zero to the Last Quantifiable Time Point (AUClast) of ARCT-810 mRNA and Lipid Components <sup>[2]</sup>
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**End point description:**

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the pharmacokinetic (PK) population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint.

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End point type	Secondary
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**End point timeframe:**

Day 1 and Day 71

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**Notes:**

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hrs*micrograms per milliliter (h*µg/mL)				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=5)	16.6 (± 30.0)			
mRNA Day 71 (n=3)	13.7 (± 32.9)			
Lipid Day 1 (n=6)	141 (± 64.7)			
Lipid Day 71 (n=3)	238 (± 27.3)			

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: The Maximum Observed Plasma Concentration (Cmax) of ARCT-810 mRNA and Lipid Components**

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End point title	The Maximum Observed Plasma Concentration (Cmax) of ARCT-810 mRNA and Lipid Components <sup>[3]</sup>
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**End point description:**

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "n" = number of participants evaluable at the specified timepoint.

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End point type	Secondary
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**End point timeframe:**

Day 1 and Day 71

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**Notes:**

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=6)	0.623 (± 121)			
mRNA Day 71 (n=3)	0.867 (± 89.5)			
Lipid Day 1 (n=6)	31.1 (± 54.1)			
Lipid Day 71 (n=3)	47.9 (± 103)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Time at which Cmax Occurred (Tmax) of ARCT-810 mRNA and Lipid Components

End point title	The Time at which Cmax Occurred (Tmax) of ARCT-810 mRNA and Lipid Components <sup>[4]</sup>
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End point description:

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "n" = number of participants evaluable at the specified timepoint.

End point type	Secondary
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End point timeframe:

Day 1 and Day 71

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hours				
median (full range (min-max))				
mRNA Day 1 (n=6)	3.06 (1.07 to 4.80)			
mRNA Day 71 (n=3)	1.00 (0.52 to 3.00)			
Lipid Day 1 (n=6)	3.15 (1.08 to 3.75)			
Lipid Day 71 (n=3)	3.00 (0.52 to 3.50)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma AUC From Time Zero Extrapolated to Infinity (AUCinf) of ARCT-810 mRNA and Lipid Components

End point title	Plasma AUC From Time Zero Extrapolated to Infinity (AUCinf) of ARCT-810 mRNA and Lipid Components <sup>[5]</sup>
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End point description:

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint.

End point type	Secondary
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End point timeframe:

Day 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=5)	17.3 (± 28.8)			
Lipid Day 1 (n=6)	145 (± 65.8)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal Half-life (T1/2) of ARCT-810 mRNA and Lipid Components

End point title	Terminal Half-life (T1/2) of ARCT-810 mRNA and Lipid Components <sup>[6]</sup>
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End point description:

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint. 9999 = data not calculable because there was insufficient data (n=2) to calculate a geometric mean.

End point type	Secondary
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End point timeframe:

Day 1 and Day 71

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hours				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=5)	51.1 (± 21.0)			
mRNA Day 71 (n=2)	9999 (± 9999)			
Lipid Day 1 (n=6)	6.11 (± 99.5)			
Lipid Day 71 (n=2)	9999 (± 9999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Body Clearance (CL) of ARCT-810 mRNA and Lipid Components

End point title	Total Body Clearance (CL) of ARCT-810 mRNA and Lipid Components <sup>[7]</sup>
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End point description:

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint. 9999 = data not calculable because there was insufficient data (n=2) to calculate a geometric mean.

End point type	Secondary
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End point timeframe:

Day 1 and Day 71

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: millilitres per hour (mL/h)				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=5)	1060 (± 42.7)			
mRNA Day 71 (n=2)	9999 (± 9999)			
Lipid Day 1 (n=6)	2440 (± 67.1)			
Lipid Day 71 (n=2)	9999 (± 9999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of Distribution at Steady State (Vss) of ARCT-810 mRNA and

## Lipid Components

End point title	Volume of Distribution at Steady State (Vss) of ARCT-810 mRNA and Lipid Components <sup>[8]</sup>
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End point description:

Pharmacokinetic parameters of ARCT-810 components (mRNA and lipid) were derived from plasma concentrations. Measured in the PK population, which included all participants who were randomized and received at least 1 complete infusion of study drug and had at least one evaluable PK result. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint. 9999 = data not calculable because there was insufficient data (n=2) to calculate a geometric mean.

End point type	Secondary
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End point timeframe:

Day 1 and Day 71

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were collected and are reported for the investigational treatment arm only.

End point values	ARCT-810			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: millilitres (mL)				
geometric mean (geometric coefficient of variation)				
mRNA Day 1 (n=5)	72300 (± 37.8)			
mRNA Day 71 (n=2)	9999 (± 9999)			
Lipid Day 1 (n=6)	12200 (± 47.4)			
Lipid Day 71 (n=2)	9999 (± 9999)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Peak Plasma Concentration for 13C-urea

End point title	Change from Baseline in Peak Plasma Concentration for 13C-urea
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End point description:

Measured in the Pharmacodynamic Evaluable Population, which included all participants who were randomized and received study drug and had completed the relevant evaluations at Baseline and at the specified time point. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Days 30, 72 and 78

End point values	ARCT-810	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: micromillimolar (µM)				
arithmetic mean (standard deviation)				
Change from Baseline at Day 30 (n=4, 2)	-0.045 (± 0.2142)	0.060 (± 0.1556)		
Change from Baseline at Day 72 (n=3, 2)	-0.120 (± 0.1997)	-0.120 (± 0.1414)		
Change from Baseline at Day 78 (n=3, 2)	0.000 (± 0.3974)	-0.090 (± 0.0141)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Area Under Curve for 13C-urea

End point title	Change from Baseline in Area Under Curve for 13C-urea
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End point description:

Measured in the Pharmacodynamic Evaluable Population, which included all participants who were randomized and received study drug and had completed the relevant evaluations at Baseline and at the specified time point. "Number of subjects analyzed" = participants evaluable for the outcome measure. "n" = number of participants evaluable at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Days 30, 72 and 78

End point values	ARCT-810	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: micromillimolar per minute (µM*min)				
arithmetic mean (standard deviation)				
Change from Baseline at Day 30 (n=4, 2)	-9.280 (± 40.6814)	9.262 (± 21.4814)		
Change from Baseline at Day 72 (n=3, 2)	-26.837 (± 43.5213)	-22.118 (± 27.5676)		
Change from Baseline at Day 78 (n=3, 2)	-9.320 (± 80.3576)	-13.427 (± 6.4458)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Area Under the Curve for 24-hour Ammonia Profile

End point title	Change from Baseline in Area Under the Curve for 24-hour Ammonia Profile
End point description: As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.	
End point type	Secondary
End point timeframe: Baseline, Day 72	

End point values	ARCT-810	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[9]</sup>	0 <sup>[10]</sup>		
Units: µM*min				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.

[10] - As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Peak Plasma Ammonia for 24-hour Ammonia Profile

End point title	Change from Baseline in Peak Plasma Ammonia for 24-hour Ammonia Profile
End point description: As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.	
End point type	Secondary
End point timeframe: Baseline, Day 72	

End point values	ARCT-810	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[11]</sup>	0 <sup>[12]</sup>		
Units: µmol/L				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.

[12] - As per updated pre-planned analysis, data were not collected for 24-hour ammonia profile.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 28 weeks

Adverse event reporting additional description:

Mortality, treatment-emergent serious and non-serious adverse events were measured in the safety population, which included all participants who were randomized and received any study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

On Day 1, participants received a single dose of placebo via intravenous infusion. Participants then received a further 5 doses of placebo on Days 15, 29, 43, 57 and 71.

Reporting group title	ARCT-810
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Reporting group description:

On Day 1, participants received a single dose of ARCT-810 via intravenous infusion. Participants then received a further 5 doses of ARCT-810 on Days 15, 29, 43, 57 and 71.

Serious adverse events	Placebo	ARCT-810	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	ARCT-810	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	6 / 6 (100.00%)	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 2	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	2 / 6 (33.33%) 3	
Ammonia increased subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 3	1 / 6 (16.67%) 1	
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 2	
Electrocardiogram ST-T segment abnormal subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	3 / 6 (50.00%) 10	
Radius fracture subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2	0 / 6 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2	1 / 6 (16.67%) 1	

Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Odynophagia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1  1 / 2 (50.00%) 1  0 / 2 (0.00%) 0  1 / 2 (50.00%) 1	2 / 6 (33.33%) 2  2 / 6 (33.33%) 2  2 / 6 (33.33%) 3  1 / 6 (16.67%) 1	
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Tenosynovitis stenosaurs subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0  0 / 2 (0.00%) 0	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1	
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)  COVID-19 subjects affected / exposed occurrences (all)  Upper respiratory tract infection	1 / 2 (50.00%) 1  0 / 2 (0.00%) 0	0 / 6 (0.00%) 0  1 / 6 (16.67%) 1	

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Varicella subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Metabolism and nutrition disorders Hyperammonaemia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2021	<p>Changes included:</p> <ul style="list-style-type: none"><li>• Section 6.2.3.1 Plasma Ammonia Levels: Deleted reference to the hyperammonemia questionnaire, as there is not one in this study. Also clarified that storage temperature for plasma samples.</li><li>• Section 7.1 Study Drug Description: Updated study drug stability data.</li><li>• Section 8.1.2 Premedication information updated</li><li>• Section 8.1.4 Anaphylaxis Precautions updated</li><li>• Appendix 1: Schedule of Assessments updated</li><li>• Appendix 2: List of Laboratory Analytes updated</li></ul>
30 September 2021	<p>Changes included:</p> <ul style="list-style-type: none"><li>• Section 5.1 Inclusion Criteria updated</li><li>• Section 6.2.4 and Appendix 1: Quality-of-life instrument was added to the protocol to include a patient-reported outcome measure prior to treatment and at the end of the 6-dose treatment course.</li></ul>
01 December 2021	<p>Changes included:</p> <ul style="list-style-type: none"><li>• Section 5.2 Exclusion Criterion updated</li><li>• Section 8.1.2 Premedication clarified</li><li>• Appendix 1 Schedule of Assessments updated</li></ul>
10 March 2022	<p>Changes included:</p> <ul style="list-style-type: none"><li>• Section 3.7 Overall Study Duration and Follow-up and Section 5.2 Exclusion Criterion updated</li><li>• Section 5.1 Inclusion Criterion updated</li><li>• Section 5.2 Exclusion Criterion and Section 8.1.1 Infection Prior to Dosing updated</li><li>• Section 5.2 Exclusion Criterion #15 updated</li></ul>

11 February 2023	<p>Changes included:</p> <ul style="list-style-type: none"> <li>• Sections 1.2.3 and 10.5.4 (Exploratory Endpoints) updated</li> <li>• Sections 2.3.1 and 2.4.4: Updated Dose/regimen Rationale and Clinical Experience sections</li> <li>• Section 2.5.2 (Risk Assessment): Table 2 safety considerations updated with new, blinded information about the ARCT-810-02 study experience.</li> <li>• Section 3.2 (Study Design): Corrected error</li> <li>• Section 3.11 (Dose Limiting Toxicity): Removed 'serious adverse event (SAE)' from the criteria for dose limiting toxicity (DLT).</li> <li>• Section 4.4 (Blinding): Clarified that if the infusion nurse is unblinded, a separate blinded person must do the visit assessments to the participant.</li> <li>• Section 5.1 Inclusion Criteria updated</li> <li>• Section 5.2 Exclusion Criteria updated</li> <li>• Section 6.1 (Study Schedule): Minor changes in wording were made</li> <li>• Section 8.1.2 (Premedication) updated</li> <li>• Sections 8.1.2, 8.1.3 (Table 5), 8.9.1, and 2.5.2 (Table 2) updated for participants who experienced an infusion-related reaction (IRR)</li> <li>• Section 8.1.3 (Infusion-Related Reactions): Added the definition of IRR and added Table 5 that includes the IRR grading system and incorporates management recommendations that were previously listed in the text. Also clarified the documentation expectations for IRR.</li> <li>• Section 8.1.4 (Anaphylaxis Precautions): Added IV cetirizine as a treatment option.</li> <li>• Section 8.3 (Study Drug Administration) and Appendix 4: The study drug infusion procedure was modified</li> <li>• Section 8.5.3 (Safety Monitoring Rules for IRR): Minor additions</li> <li>• Appendix 1: Schedule of Assessments updated</li> <li>• Appendix 2: List of Laboratory Analytes updated</li> </ul>
16 June 2023	<p>Changes included:</p> <ul style="list-style-type: none"> <li>• Section 2.3.1 Dose and Regimen: Removed redundant information on IRRs and updated the initial infusion procedure.</li> <li>• Section 2.4.2.2 Drug Product ARCT-810: Changed the title of Figure 3 to correct the description of what is presented.</li> <li>• Section 2.4.4 Clinical Experience: Edited the information to include updated safety data from ongoing studies.</li> <li>• Section 2.5.2 Risk Assessment: Edited the information to include updated information on IRRs from the ongoing studies; added revised mitigation procedures to reduce risk.</li> <li>• Section 3.2 Study Design: Updated cohort and dose information. Changed the Screening duration to be at least 4 weeks with no maximum duration.</li> <li>• Section 3.7 Overall Study Duration and Follow-up: Specified that Screening duration must be at least 4 weeks, allowing extensions for flexibility. Deleted unnecessary language.</li> <li>• Section 3.11 Dose-Limiting Toxicity: Clarified the definition of a DLT.</li> <li>• Section 3.13 Study Stopping Rules: Removed contradictory wording and clarified rules for terminating the study based on discussions with the Safety Review Committee (SRC) after the occurrence of the suspected unexpected serious adverse reaction in this study.</li> <li>• Section 8.1 Infection prior to dosing: Specified that if Screening needs to be extended beyond 6 weeks, the medical monitor should be consulted on whether any assessments need to be repeated prior to the first dose.</li> <li>• Section 8.1.2 Premedication: Updated</li> <li>• Section 8.1.4 Anaphylaxis Procedures: Updated</li> <li>• Section 8.5.1 Safety Monitoring Rules for Liver Chemistry Tests updated</li> <li>• Appendix 1 Schedule of Assessments updated</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated based on the sponsor's decision around enrollment rate prior to initiating Cohort B.

Notes: