Clinical trial results:
A Phase 1/2 Open-label Study in Patients with Arginase I Deficiency to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous AEB1102

Summary

EudraCT number	2017-003851-45
Trial protocol	GB PT
Global end of trial date	28 February 2019

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	CAEB1102-101A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02488044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aeglea BioTherapeutics, Inc.
Sponsor organisation address	805 Las Cimas Parkway, Suite 100, Austin, United States, 78736
Public contact	Arg1-D Trial Information, Aeglea Biotherapeutics, Inc., +1 512 942-2935, raredisease@aegleabio.com
Scientific contact	Arg1-D Trial Information, Aeglea Biotherapeutics, Inc., +1 512 942-2935, raredisease@aegleabio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2019
Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of intravenous (IV) administration of AEB1102 in patients with Arginase I deficiency and hyperargininemia

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and local regulations. The protocol, all amendments and the informed consent forms (ICFs) / patient information sheets (PIS) were reviewed and approved relevant ethics committee (EC) in each participating country.

Background therapy:

All 16 patients included in the trial were managed prior to and during the study with dietary protein restriction and essential amino acid supplementation, and 14 patients were also taking ammonia scavengers prior to and during the study. Patients had individual elevated mean plasma arginine levels ranging from 238 to 566 µM at baseline prior to pegzilarginase treatment.

Evidence for comparator:

No comparator used

Actual start date of recruitment	25 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	16
EEA total number of subjects	3

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)	6
Adolescents (12-17 years)	5
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted globally and enrolled subjects at 9 clinical sites
• 6 centers in the United States (US)
• 1 center in the United Kingdom (UK)
• 1 center in Portugal
• 1 center in Canada

Pre-assignment

Screening details:

Eligibility for the study was determined during the screening period, which was up to 6 weeks in duration. Subjects who signed the ICF, were assigned a unique subject identification and were screened. The total number of subjects who were screened was 17, and 1 of those subjects did not enter the study. A total of 16 subjects were eligible.

Pre-assignment period milestones

Number of subjects started	17[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet the eligibility criteria: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 17 subjects were screened, 1 subject did not meet the eligibility criteria, 16 subject were enrolled into the study.

Period 1

Period 1 title	Single Ascending Dose Escalation
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AEB1102 Period 1

Arm description:

Each patient received single ascending doses of study drug with a 2-week washout/observation period between successive dose levels. For each individual subject, dose escalation continued in pre-defined steps until stopping rules were met or the highest allowed dose of 0.30 mg/kg was reached.

Arm type	Experimental
Investigational medicinal product name	Pegzilarginase
Investigational medicinal product code	AEB1102
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Part 1 doses: Each subject received escalating doses of study drug in Part 1 with a 2-week washout/observation period between each successive dose level. The possible doses for each subject in Part 1 were 0.015, 0.03, 0.06, 0.10, 0.15, 0.20, and 0.30 mg/kg, at 2-week intervals as needed to optimize plasma arginine (over a maximum of 14 weeks).

Number of subjects in period 1	AEB1102 Period 1
Started	16
Completed	15
Not completed	1
Consent withdrawn by subject	1

Period 2	
Period 2 title	Repeat Dosing
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AEB1102 Period 2

Arm description:

This was a repeat-dosing period for subjects who completed Part 1 without a clinically significant reason to preclude continued dosing with study drug. Each patient received 8 weekly repeat doses of study drug with the starting dose chosen based on dose response from Part 1.

Arm type	Experimental
Investigational medicinal product name	Pegzilarginase
Investigational medicinal product code	AEB1102
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Part 2: Part 2 was a repeat-dosing period for subjects who completed Part 1 without a clinically significant reason to preclude continued dosing of study drug. The starting dose level was based on PK of study drug and plasma arginine levels from single- and repeat-dose results available at the time the subject completed Part 1. No doses in Part 2 exceeded the highest dose used in any subject in Part 1 (Once weekly for a period of 7 weeks (8 doses)

Number of subjects in period 2	AEB1102 Period 2
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Single Ascending Dose Escalation

Reporting group description:

A total of 16 subjects were eligible to participate in the study, received study drug, and were included in the Full Analysis Set. Baseline data for this group applied to both periods.

Reporting group values	Single Ascending Dose Escalation	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	15		
full range (min-max)	5 to 31	-	
Gender categorical			
A majority (68.75%) of the subjects were female (11 female subjects, 5 male subjects).			
Units: Subjects			
Female	11	11	
Male	5	5	
Race Units: Subjects			
Asian	2	2	
Black/African American	1	1	
White	11	11	
Other	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	7	7	
Documented developmental delay Units: Subjects			
Yes	9	9	
No	7	7	
Seizures Units: Subjects			
Yes	4	4	

No	12	12	
Level of spacticity Units: Subjects			
None	4	4	
Mild	3	3	
Moderate	5	5	
Severe	4	4	
Plasma arginine Units: Subjects			
> 200 umol/L	16	16	
Age at inital symptoms			
Results available for 5 subjects			
Units: Years			
median	7.1		
full range (min-max)	5.6 to 17.7	-	
Age at genetic diagnosis			
Results available for 15 subjects			
Units: Years			
median	3.6		
full range (min-max)	0 to 7.6	-	
Arginase activity in red blood cells Units: percent			
median	0.1		
full range (min-max)	0 to 15	-	
Plasma Arginine Units: uM			
median	389		
full range (min-max)	238 to 566	-	
Ammonia Units: uM			
median	38		
full range (min-max)	9 to 77	-	
Plasma a-N-acetylarginine Units: umol/L			
median	1.2		
full range (min-max)	0.3 to 1.8	-	
Alanine amino transferase Units: U/L			
median	34		
full range (min-max)	15 to 171	-	
Aspartate aminotransferase Units: U/L			
median	38		
full range (min-max)	25 to 63	-	
Number of hyperammonemic episodes last month Units: number			
median	0		
full range (min-max)	0 to 1	-	
Number of hyperammonemic episodes last year Units: number			

median	0		
full range (min-max)	0 to 6	-	
Height Units: cm			
median	142.5		
full range (min-max)	107.5 to 166.4	-	
Height Units: Centiles			
median	6.7		
full range (min-max)	0 to 59.6	-	
Ornithine Units: umol/L			
median	18		
full range (min-max)	12.5 to 31.6	-	
a-keto-d-guanidinovaleric acid Units: umol/L			
median	4.8		
full range (min-max)	3.07 to 7.17	-	
Argininic Acid Units: (umol/L)			
median	2.4		
full range (min-max)	1.64 to 6.33	-	
Guanidinoacetic Acid Units: umol/L			
median	2.7		
full range (min-max)	1.54 to 5.07	-	

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all subjects who received study drug. The FAS was used for evaluating subject characteristics, study drug administration, and safety endpoints.
The Pharmacodynamic Analysis Set (PD Set) included all subjects in the FAS who were enrolled (consented) in the study and had any valid arginine concentration-time data. All subjects in the FAS were also in the PD Set; therefore, separate analyses were not performed for the PD Set.

Reporting group values	Full analysis set		
Number of subjects	16		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	6		
Adolescents (12-17 years)	5		
Adults (18-64 years)	5		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years			
median	15		
full range (min-max)	5 to 31		
Gender categorical			
A majority (68.75%) of the subjects were female (11 female subjects, 5 male subjects).			
Units: Subjects			
Female	11		
Male	5		
Race Units: Subjects			
Asian	2		
Black/African American	1		
White	11		
Other	2		
Ethnicity Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	7		
Documented developmental delay Units: Subjects			
Yes	9		
No	7		
Seizures Units: Subjects			
Yes	4		
No	12		
Level of spacticity Units: Subjects			
None	4		
Mild	3		
Moderate	5		
Severe	4		
Plasma arginine Units: Subjects			
> 200 umol/L	16		
Age at inital symptoms			
Results available for 5 subjects			
Units: Years			
median	7.1		
full range (min-max)	5.6 to 17.7		
Age at genetic diagnosis			
Results available for 15 subjects			
Units: Years			
median	3.6		
full range (min-max)	0 to 7.6		
Arginase activity in red blood cells Units: percent			
median	0.1		
full range (min-max)	0 to 15		
Plasma Arginine			

Units: uM			
median	389		
full range (min-max)	238 to 566		
Ammonia			
Units: uM			
median	38		
full range (min-max)	9 to 77		
Plasma a-N-acetylarginine			
Units: umol/L			
median	1.2		
full range (min-max)	0.3 to 1.8		
Alanine amino transferase			
Units: U/L			
median	34		
full range (min-max)	15 to 171		
Aspartate aminotransferase			
Units: U/L			
median	38		
full range (min-max)	25 to 63		
Number of hyperammonemic episodes last month			
Units: number			
median	0		
full range (min-max)	0 to 1		
Number of hyperammonemic episodes last year			
Units: number			
median	0		
full range (min-max)	0 to 6		
Height			
Units: cm			
median	142.5		
full range (min-max)	107.5 to 166.4		
Height			
Units: Centiles			
median	6.7		
full range (min-max)	0 to 59.6		
Ornithine			
Units: umol/L			
median	18		
full range (min-max)	12.5 to 31.6		
a-keto-d-guanidinovaleric acid			
Units: umol/L			
median	4.8		
full range (min-max)	3.07 to 7.17		
Argininic Acid			
Units: (umol/L)			
median	2.4		
full range (min-max)	1.64 to 6.33		
Guanidinoacetic Acid			
Units: umol/L			
median	2.7		

full range (min-max)	1.54 to 5.07		

End points

End points reporting groups

Reporting group title	AEB1102 Period 1

Reporting group description:

Each patient received single ascending doses of study drug with a 2-week washout/observation period between successive dose levels. For each individual subject, dose escalation continued in pre-defined steps until stopping rules were met or the highest allowed dose of 0.30 mg/kg was reached.

Reporting group title	AEB1102 Period 2

Reporting group description:

This was a repeat-dosing period for subjects who completed Part 1 without a clinically significant reason to preclude continued dosing with study drug. Each patient received 8 weekly repeat doses of study drug with the starting dose chosen based on dose response from Part 1.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all subjects who received study drug. The FAS was used for evaluating subject characteristics, study drug administration, and safety endpoints.
The Pharmacodynamic Analysis Set (PD Set) included all subjects in the FAS who were enrolled (consented) in the study and had any valid arginine concentration-time data. All subjects in the FAS were also in the PD Set; therefore, separate analyses were not performed for the PD Set.

Primary: Number of subjects with Adverse Events

End point title	Number of subjects with Adverse Events[1]

End point description:

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug. Treatment-emergent adverse events (TEAEs) were defined as those events which are newly occurring or worsening from Baseline (ie, on or after the first dose of study drug). All TEAEs were coded using MedDRA Version 19.0 terminology. The incidence of AEs was summarized and tabulated by MedDRA SOC and PT.

End point type	Primary

End point timeframe:

Weekly throughout the study, from screening up to week 14 plus FUP in Period 1 and up to week 8 plus FUP in Period 2

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed. For detailed breakdown of AEs see Adverse events section.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: Number				
Any TEAE	16			
Study drug-related TEAE	13			
TEAEs requiring dose reduction	0			
TEAEs requiring dose interruption	6			
TEAEs leading to discontinuation of study drug	0			
Study drug-related TEAEs leading to discontinuatio	0			
TEAEs with fatal outcome	0			
Any SAE	8			

Study drug-related SAE	5			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse Events by Maximum Severity

End point title	Adverse Events by Maximum Severity[2]

End point description:

End point type	Primary

End point timeframe:

Weekly throughout the study, from screening up to week 14 plus FUP in Period 1 and up to week 8 plus FUP in Period 2

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: No statistical analysis was performed. For detailed break down of AEs see Adverse events section.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: Number				
Mild	4			
Moderate	10			
Severe	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Baseline to week 14

End point values	AEB1102 Period 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: T1/2 (hr)				
arithmetic mean (standard deviation)				
0.015 mg/kg	30.5 (± 11.8)			
0.03 mg/kg	21.0 (± 9.47)			
0.06 mg/kg	26.7 (± 9.5)			

Attachments (see zip file)	Summary of PK parameters Part 1/Summary PK Parameters in Summary of PK parameters Part 2/Summary PK Parameters in Concentration versus Time Profile Part 1/Mean (±SD) AEB1102 Concentration versus Time Profile Part 2/Mean (±SD) AEB1102

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Baseline to week 14

End point values	AEB1102 Period 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Tmax (hr)				
median (full range (min-max))				
0.015 mg/kg	0.342 (0.183 to 8.28)			
0.03 mg/kg	0.884 (0.217 to 4.28)			
0.06 mg/kg	0.383 (0.167 to 4.20)			

0.1 mg/kg	0.667 (0.233 to 4.02)			
0.2 mg/kg	0.567 (0.567 to 0.567)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Baseline to week 14

End point values	AEB1102 Period 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Cmax (ug/mL)				
arithmetic mean (standard deviation)				
0.015 mg/kg	0.428 (± 0.0915)			
0.03 mg/kg	0.723 (± 0.247)			
0.06 mg/kg	1.73 (± 0.538)			
0.1 mg/kg	2.27 (± 0.238)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Baseline to week 14

End point values	AEB1102 Period 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: AUC 0-168 (hr*ug/mL)				
arithmetic mean (standard deviation)				
0.015 mg/kg	18.2 (± 7.33)			
0.03 mg/kg	26.5 (± 14.6)			
0.06 mg/kg	63.0 (± 29.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 1 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: T1/2 (hr)				
arithmetic mean (standard deviation)				
0.06 mg/kg	31.5 (± 2.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 1 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Tmax (hr)				
median (full range (min-max))				
0.04 mg/kg	0.300 (0.300 to 2.55)			
0.06 mg/kg	0.250 (0.183 to 4.00)			
0.09 mg/kg	4.00 (4.00 to 4.00)			
0.1 mg/kg	4.25 (4.25 to 4.25)			
0.12 mg/kg	1.20 (0.333 to 1.20)			
0.015 mg/kg	1.00 (1.00 to 1.00)			
0.03 mg/kg	0.617 (0.617 to 0.617)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 1 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Cmax (ug/mL)				
arithmetic mean (standard deviation)				
0.04 mg/kg	1.01 (± 0221)			
0.06 mg/kg	1.75 (± 0.391)			
0.12 mg/kg	2.87 (± 0.626)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 1 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: AUC 1-168 (hr*ug/mL)				
arithmetic mean (standard deviation)				
0.06 mg/kg	82.5 (± 16.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:
Week 8 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: T 1/2 (hr)				
arithmetic mean (standard deviation)				
0.12 mg/kg	33.8 (± 7.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:
Week 8 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Tmax (hr)				
median (full range (min-max))				
0.04 mg/kg	0.259 (0.217 to 0.300)			
0.06 mg/kg	0.350 (0.250 to 4.00)			
0.09 mg/kg	0.300 (0.250 to 0.350)			
0.1 mg/kg	8.35 (8.35 to 8.35)			
0.12 mg/kg	0.300 (0.233 to 2.17)			
0.2 mg/kg	0.433 (0.433 to 0.433)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 8 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Cmax (ug/mL)				
arithmetic mean (standard deviation)				
0.06 mg/kg	1.66 (± 0.406)			
0.12 mg/kg	3.52 (± 1.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic evaluation of AEB1102

End point title	Pharmacokinetic evaluation of AEB1102

End point description:

Serum concentration versus time data were analyzed by noncompartmental analysis (NCA) with PhoenixTM WinNonlin® Version 8.0, using an IV infusion administration model. Actual (elapsed) sampling, actual infusion times and dose assignments in the clinical database were used in the analysis; when there was missing dosing or sampling information (and the actual time could not be calculated), the corresponding nominal time(s) was used.

End point type	Secondary

End point timeframe:

Week 8 Part 2

End point values	AEB1102 Period 2			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: AUC 1-168 (hr*ug/mL)				
arithmetic mean (standard deviation)				
0.12 mg/kg	145 (± 31.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for non-serious AEs and SAEs was the period from the first dose of study drug continuing through the last study Follow-up Visit (weekly throughout the study, up to week 14 in Part 2)

Adverse event reporting additional description:

The Investigator assessed AEs for severity, for relationship to study drug (not related, unlikely, possibly related, probably related, or definitely related), and whether the event met one or more of the definitions of an SAE. Adverse events reported spontaneously by the subject, in response to an open-ended question, or revealed by observation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Full Analysis Set

Reporting group description:

The Full Analysis Set (FAS) included all subjects who received at least one dose of study medication. The FAS was used for evaluating subject characteristics, treatment administration, and safety endpoints.

Serious adverse events	Full Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperammonemia			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Full Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Infusion site pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Crying			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	6		
Anaphylactic reaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Mood altered			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Blood potassium increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood urea decreased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Cardiac murmur			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Coagulation test abnormal			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Stoma site pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 5 1 / 16 (6.25%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Lip dry subjects affected / exposed occurrences (all)	8 / 16 (50.00%) 9 3 / 16 (18.75%) 5 2 / 16 (12.50%) 4 2 / 16 (12.50%) 2 1 / 16 (6.25%) 1		

Constipation subjects affected / exposed occurrences (all) Faeces soft subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 2 1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Skin ulcer subjects affected / exposed occurrences (all)	 4 / 16 (25.00%) 4 2 / 16 (12.50%) 2 1 / 16 (6.25%) 1		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 2 / 16 (12.50%) 2 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		

Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Ear infection			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Mononucleosis syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperammonemia			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	9		
Decreased appetite			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2016	Amendment 1 (US only): Addressed comments received from the US FDA and clarified the timing of study procedures
01 November 2016	Amendment 2 (US and Canada only): Converted the study into a Phase 1/2 study that increased the potential maximum dose that a subject could have received in the dose-escalation period, thereby increasing the total number of single escalating doses to 7 from the current 4, added a repeat-dose phase, and expanded enrollment to include pediatric subjects.
30 June 2017	Amendment 2.1 (US and UK only): Specified DSMB assessment of specific clinical data from subjects aged ≥ 14 years at informed consent prior to dosing the youngest subjects (aged 2 to 13 years) in Parts 1 and 2. • Minor revisions were made to objectives and endpoints, PK sampling, and sample collection times.
31 December 2017	Amendment 2.2 (UK only): Addressed requests from the MHRA in the UK regarding language related to birth control requirements for female and male subjects and language related to the potential (based on animal studies) for testicular toxicity in male study subjects
23 January 2018	Amendment 2.3 (US only): Provided for dosing adjustments in response to infusion-related adverse events, in particular, hypersensitivity reactions. Additionally, stricter language was added regarding birth control requirements for female and male subjects.
17 May 2018	Amendment 3 (Global): Harmonised several other amendments (2.0, 2.2, and 2.3) that were active in different countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported