Clinical trial results:
Phase III, randomized, double-blind, placebo controlled, parallel-group, study of AB103 as compared to placebo in patients with necrotizing soft tissue infections (NSTI)

Summary

EudraCT number	2018-001125-15
Trial protocol	FR
Global end of trial date	18 October 2019

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	ATB-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02469857
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Atox Bio Ltd.
Sponsor organisation address	8 Pinhas Sapir St., Ness Ziona, Israel, 7403631
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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	17 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of AB103 as compared to placebo, in patients diagnosed with NSTI, using a clinical composite success endpoint (NICCE score)

Protection of trial subjects:

Good clinical practices were utilized in the conduct of this trial, including appropriate informed consent procedures and required documentation and reporting of adverse events.

Safety data obtained during study visits associated with Study Days 1, 2, 3, 7, 10, 14, 21, and 28 were systematically assessed throughout the study. In addition, data from spontaneously reported AEs were included in safety assessments. Data associated with deaths and study drug-related serious adverse events (SAEs) were collected from study drug administration though the Day 90 visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
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	United States: 273
Country: Number of subjects enrolled	France: 17
Worldwide total number of subjects	290
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	212

From 65 to 84 years	72
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Initiation of clinical investigative sites in the US began in September 2015 and new sites were recruited and initiated through November 2018. The last sites to be initiated were in France. Since NSTI is an acute life-threatening infection patients were only identified at the time of hospital presentation and not recruited pre-hospital admission.

Pre-assignment

Screening details:

Screening started once a clinical diagnosis of NSTI was entertained and a decision for urgent surgical wound exploration and debridement was made. A total of 319 patients were randomized; however, 29 patients were not dosed (did not have NSTI or failed reassessment of eligibility criteria).

Pre-assignment period milestones

Number of subjects started	319[1]
Intermediate milestone: Number of subjects	Randomized and Treated: 290
Number of subjects completed	290

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not have NSTI or did not meet entry criteria: 29

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: The clinical sites had only 6 hours from time of decision to take a patient with suspected NSTI to the OR and obtain surgical confirmation of NSTI to initiate infusion of study drug. Given this very short timeline and the critical need to get pts to the OR to avoid further progression of disease, sites were allowed to randomize subjects so that study drug could be ready once surgical confirmation of NSTI disease was obtained. If no NSTI then pts were considered screen failures and not dosed.

Period 1

Period 1 title	Treatment and Follow Up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Reltecimod 0.5 mg/kg

Arm description:

Reltecimod 0.5 mg/kg total body weight administered once as an intravenous infusion over approximately 10 minutes

Arm type	Experimental
Investigational medicinal product name	Reltecimod
Investigational medicinal product code	
Other name	AB-102
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each vial contains 10.5 mg of Reltecimod. Prior to use, each vial of drug product (10.5 mg Reltecimod) is reconstituted in 10.5 mL of water for injection to generate a peptide concentration of 1 mg/mL. The reconstituted drug product is administered directly and is not diluted prior to administration. To prepare the drug quantity needed for infusion, the contents of several vials are pooled together by the study pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual

institution), under sterile conditions plus adequate priming volume of the IV line. The number of vials would depend on the patient's weight, in order to achieve a dose of 0.5 mg/kg. The Reltecimod drug product will be administered at a dose of 0.5 mg/kg via a syringe pump in a separate catheter as a single intravenous infusion given over 10 minutes.

Arm title	Placebo

Arm description:

Normal saline (0.9% sodium chloride solution) administered once as an intravenous infusion over approximately 10 minutes

Arm type	Placebo
Investigational medicinal product name	0.9% Sterile Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Placebo will be pyrogen-free, preservative-free sterile 0.9% saline, USP administered as a single infusion at a volume calculated and based on patient weight, 0.5 mL/kg (a volume equivalent with Reltecimod dosing schema), plus adequate priming volume of the IV line.

Number of subjects in period 1	Reltecimod 0.5 mg/kg	Placebo
Started	143	147
Completed	142	144
Not completed	1	3
Consent withdrawn by subject	-	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Reltecimod 0.5 mg/kg
Reporting group description:	
Reltecimod 0.5 mg/kg total body weight administered once as an intravenous infusion over approximately 10 minutes	
Reporting group title	Placebo
Reporting group description:	
Normal saline (0.9% sodium chloride solution) administered once as an intravenous infusion over approximately 10 minutes	

Reporting group values	Reltecimod 0.5 mg/kg	Placebo	Total
Number of subjects	143	147	290
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)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	53.4	56.3	
standard deviation	± 15.3	± 15.0	-
Gender categorical Units: Subjects			
Female	58	59	117
Male	85	88	173
Ethnicity Units: Subjects			
Hispanic or Latino	10	11	21
Not Hispanic or Latino	131	133	264
Missing	2	3	5
Race Units: Subjects			
White	106	110	216
Black or African American	23	24	47
American Indian or Alaska Native	3	2	5
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	1	1
Other	4	4	8
Missing	5	6	11

Region of Enrollment			
This characteristic represents the two countries from which patients were enrolled into this study and received study drug (i.e., United States and France).			
Units: Subjects			
United States	135	138	273
France	8	9	17
NSTI Diagnosis Units: Subjects			
Necrotizing Fasciitis	96	95	191
Fournier's Gangrene	43	40	83
Gas Gangrene/Myonecrosis	1	4	5
Other NSTI	3	8	11
Comorbidities: Diabetes Units: Subjects			
Diabetes	64	59	123
No Diabetes	79	88	167
Sepsis Presentation: Cardiovascular Organ Failure			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline. Categories are NOT mutually exclusive.			
Units: Subjects			
Cardiovascular Organ Failure	81	62	143
No Cardiovascular Organ Failure	62	85	147
Acute Kidney Injury (AKI) Presentation			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline.			
Units: Subjects			
Any AKI at Screening	87	103	190
No AKI at Screening	56	44	100
Sepsis Presentation: Respiratory Organ Failure			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline.			
Units: Subjects			
Respiratory Organ Failure	19	11	30
No Respiratory Organ Failure	124	136	260
Comorbidities: Cardiovascular Disease Units: Subjects			
Cardiovascular Disease	37	28	65
No Cardiovascular Disease	106	119	225
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	31.4	33.7	
standard deviation	± 8.3	± 8.3	-
Modified Sequential Organ Failure Assessment (mSOFA) Score			
Modified Sequential Organ Failure Assessment (mSOFA) total scores range from 0 to 20, with higher scores reflecting a worse clinical status or outcome. An mSOFA total score of 0 or 1 reflects resolution of organ dysfunction/failure.			

Units: none			
arithmetic mean	5.6	5.4	
standard deviation	± 2.5	± 2.2	-
Acute Physiology and Chronic Health Evaluation II (APACHE II) Score			
The Acute Physiology and Chronic Health Evaluation (APACHE) Score is a severity of illness classification system. It is determined within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements (physiologic variables, age, chronic health status). Higher scores correspond to more severe disease and a greater risk of death.			
Units: none			
arithmetic mean	16.4	16.4	
standard deviation	± 6.8	± 6.6	-

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)-Reltecimod
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set: The FAS was used in primary efficacy analyses and included patients in the mITT analysis set assigned according to actual treatment received, and excluding patients with significant pre-randomization violations of inclusion/exclusion criteria that prevent patients from achieving the primary endpoint or that substantially confound estimates of drug effects

Subject analysis set title	Full Analysis Set (FAS)-Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set: The FAS was used in primary efficacy analyses and included patients in the mITT analysis set assigned according to actual treatment received, and excluding patients with significant pre-randomization violations of inclusion/exclusion criteria that prevent patients from achieving the primary endpoint or that substantially confound estimates of drug effects

Reporting group values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo	
Number of subjects	133	144	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	53.3	56.5	
standard deviation	± 15.4	± 14.9	
Gender categorical			
Units: Subjects			
Female	55	59	
Male	78	85	

Ethnicity Units: Subjects			
Hispanic or Latino	8	11	
Not Hispanic or Latino	123	130	
Missing	2	3	
Race Units: Subjects			
White	97	108	
Black or African American	22	23	
American Indian or Alaska Native	3	2	
Asian	2	0	
Native Hawaiian or Other Pacific Islander	0	1	
Other	4	4	
Missing	5	6	
Region of Enrollment			
This characteristic represents the two countries from which patients were enrolled into this study and received study drug (i.e., United States and France).			
Units: Subjects			
United States	126	135	
France	7	9	
NSTI Diagnosis Units: Subjects			
Necrotizing Fasciitis	88	93	
Fournier's Gangrene	41	39	
Gas Gangrene/Myonecrosis	1	4	
Other NSTI	3	8	
Comorbidities: Diabetes Units: Subjects			
Diabetes	57	58	
No Diabetes	76	86	
Sepsis Presentation: Cardiovascular Organ Failure			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline. Categories are NOT mutually exclusive.			
Units: Subjects			
Cardiovascular Organ Failure	80	62	
No Cardiovascular Organ Failure	53	82	
Acute Kidney Injury (AKI) Presentation			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline.			
Units: Subjects			
Any AKI at Screening	82	102	
No AKI at Screening	51	42	
Sepsis Presentation: Respiratory Organ Failure			
Sepsis presentation focuses on the number of patients with cardiovascular failure and the number of patients with respiratory failure at baseline. Some patients had both cardiovascular and respiratory failure at baseline, some patients had either cardiovascular or respiratory failure at baseline, and some patients had neither at baseline.			

Units: Subjects			
Respiratory Organ Failure	19	11	
No Respiratory Organ Failure	114	133	
Comorbidities: Cardiovascular Disease Units: Subjects			
Cardiovascular Disease	34	28	
No Cardiovascular Disease	99	116	
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	31.3	33.7	
standard deviation	± 8.4	± 8.4	
Modified Sequential Organ Failure Assessment (mSOFA) Score			
Modified Sequential Organ Failure Assessment (mSOFA) total scores range from 0 to 20, with higher scores reflecting a worse clinical status or outcome. An mSOFA total score of 0 or 1 reflects resolution of organ dysfunction/failure.			
Units: none			
arithmetic mean	5.6	5.5	
standard deviation	± 2.5	± 2.2	
Acute Physiology and Chronic Health Evaluation II (APACHE II) Score			
The Acute Physiology and Chronic Health Evaluation (APACHE) Score is a severity of illness classification system. It is determined within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements (physiologic variables, age, chronic health status). Higher scores correspond to more severe disease and a greater risk of death.			
Units: none			
arithmetic mean	16.4	16.6	
standard deviation	± 6.8	± 6.5	

End points

End points reporting groups

Reporting group title	Reltecimod 0.5 mg/kg
Reporting group description:	
Reltecimod 0.5 mg/kg total body weight administered once as an intravenous infusion over approximately 10 minutes	
Reporting group title	Placebo
Reporting group description:	
Normal saline (0.9% sodium chloride solution) administered once as an intravenous infusion over approximately 10 minutes	
Subject analysis set title	Full Analysis Set (FAS)-Reltecimod
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set: The FAS was used in primary efficacy analyses and included patients in the mITT analysis set assigned according to actual treatment received, and excluding patients with significant pre-randomization violations of inclusion/exclusion criteria that prevent patients from achieving the primary endpoint or that substantially confound estimates of drug effects	
Subject analysis set title	Full Analysis Set (FAS)-Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set: The FAS was used in primary efficacy analyses and included patients in the mITT analysis set assigned according to actual treatment received, and excluding patients with significant pre-randomization violations of inclusion/exclusion criteria that prevent patients from achieving the primary endpoint or that substantially confound estimates of drug effects	

Primary: Necrotizing Infections Clinical Composite Endpoint (NICCE)

End point title	Necrotizing Infections Clinical Composite Endpoint (NICCE)
End point description:	
Necrotizing Infections Clinical Composite Endpoint (NICCE) was made up of the following 5 components, all of which had to be met to successfully achieve the primary outcome measure: (i) Alive at Day 28, (ii) ≤ 3 debridements through Day 14, (iii) No amputation performed after the first debridement, (iv) Day 14 modified Sequential Organ Failure Assessment (mSOFA) score ≤ 1, and (v) Reduction of ≥ 3 mSOFA score points between Baseline and Day 14. This analysis was done in the modified intent-to-treat analysis set (mITT) (i.e., all randomized patients who were exposed to study drug [reltecimod or placebo] and who had a confirmed surgical diagnosis of NSTI, with patients analyzed according to their randomized treatment assignment) and in the Full Analysis Set (FAS) (patients who met the mITT criteria but who did not have a violation of an inclusion or exclusion criterion that prevented achievement of the primary efficacy endpoint and were analyzed according to treatment received.	
End point type	Primary
End point timeframe:	
28 days	

End point values	Reltecimod 0.5 mg/kg	Placebo	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	143	147	133	144
Units: subjects	69	59	70	58

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis (NICCE-mITT population)
Statistical analysis description:	
Responder analysis with success assigned as patients meeting all the 5 components of the composite endpoint and failure assigned as patients not meeting any one or more of the 5 components of the composite endpoint.	
Comparison groups	Reltecimod 0.5 mg/kg v Placebo
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	23.7

Statistical analysis title	Primary Efficacy Analysis (NICCE-FAS Population)
Statistical analysis description:	
Responder analysis with success assigned as patients meeting all the 5 components of the composite endpoint and failure assigned as patients not meeting any one or more of the 5 components of the composite endpoint.	
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	277
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.039
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	24

Secondary: Intensive care unit (ICU)-free Days

End point title	Intensive care unit (ICU)-free Days

End point description:

Days that patents are alive and not in the ICU calculated using a 28 day period from receipt of study medication. More free days is considered a positive outcome

End point type	Secondary

End point timeframe:

28 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	144		
Units: Days				
median (full range (min-max))	20 (0 to 28)	18 (0 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilator-free days

End point title	Ventilator-free days

End point description:

Days that patient are alive and not requiring mechanical ventilation support calculated over a 28 day period from receipt of study medication. More free days is considered a positive outcome.

End point type	Secondary

End point timeframe:

28 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	144		
Units: Days				
median (full range (min-max))	22 (0 to 28)	21 (0 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Days

End point title	Hospital Days

End point description:

Number of days that the patient is hospitalized with less hospital days considered the desired outcome

End point type	Secondary

End point timeframe:

Duration of hospitalization

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	144		
Units: Days				
median (full range (min-max))	19 (1 to 103)	20 (2 to 135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Discharge Location

End point title	Hospital Discharge Location

End point description:

Number of patients with favorable discharge location (home or rehabilitation facility) or less than favorable discharge location (skilled nursing facility, another acute care facility, death, other)

End point type	Secondary

End point timeframe:

90 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	144		
Units: Patients				
Favorable Discharge Location	81	71		
Less Than Favorable Discharge Location	52	73		

Statistical analyses

Statistical analysis title	Hospital Discharge Location

Statistical analysis description:	
Comparison of reltecimod versus placebo by Favorable Discharge Location	
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	277
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.053
Method	Chi-squared

Secondary: Day 0 Through Day 90 Mortality

End point title	Day 0 Through Day 90 Mortality
End point description:	
Cumulative mortality (number of deaths) occurring from Day 0 through Day 90	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	144		
Units: Patients	22	29		

Statistical analyses

Statistical analysis title	Cumulative Mortality Day 0-90
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.43

Notes:

[1] - Study was not powered to assess Day 0-90 mortality rate comparison between reltecimod and placebo. Provide hazard ratio with 95% CIs.

Secondary: Day 14 mSOFA <=1

End point title	Day 14 mSOFA <=1

End point description:

Patients achieving resolution of organ dysfunction at Day 14, defined as a mSOFA score <=1

End point type	Secondary

End point timeframe:

14 Days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133[2]	144[3]		
Units: Patients	89	79		

Notes:

[2] - Reltecimod patients in FAS analysis set

[3] - Placebo patients in FAS analysis set

Statistical analyses

Statistical analysis title	Day 14 mSOFA <=1
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	23.5

Other pre-specified: NICCE in Patients with Baseline mSOFA >=5

End point title	NICCE in Patients with Baseline mSOFA >=5

End point description:

Necrotizing Infections Clinical Composite Endpoint (NICCE) was made up of the following 5 components, all of which had to be met to successfully achieve the primary outcome measure: (i) Alive at Day 28, (ii) ≤ 3 debridements through Day 14, (iii) No amputation performed after the first debridement, (iv) Day 14 modified Sequential Organ Failure Assessment (mSOFA) score ≤ 1, and (v) Reduction of ≥ 3 mSOFA score points between Baseline and Day 14.

End point type	Other pre-specified

End point timeframe:

28 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[4]	87[5]		
Units: Patients	40	32		

Notes:

[4] - Reltecimod patients in FAS with mSOFA >=5 at baseline

[5] - Placebo patients in FAS with mSOFA >=5 at baseline

Statistical analyses

Statistical analysis title	NICCE analysis

Statistical analysis description:

Responder analysis with success assigned as patients meeting all the 5 components of the composite endpoint and failure assigned as patients not meeting any one or more of the 5 components of the composite endpoint.

Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	29.5

Other pre-specified: NICCE Among Patients with Shock at Baseline

End point title	NICCE Among Patients with Shock at Baseline

End point description:

Necrotizing Infections Clinical Composite Endpoint (NICCE) was made up of the following 5 components, all of which had to be met to successfully achieve the primary outcome measure: (i) Alive at Day 28, (ii) ≤ 3 debridements through Day 14, (iii) No amputation performed after the first debridement, (iv) Day 14 modified Sequential Organ Failure Assessment (mSOFA) score ≤ 1, and (v) Reduction of ≥ 3 mSOFA score points between Baseline and Day 14.

End point type	Other pre-specified

End point timeframe:

28 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[6]	62[7]		
Units: Patients	40	24		

Notes:

[6] - Reltecimod patients in FAS with shock at basline

[7] - Placebo patients in FAS with shock at baseline

Statistical analyses

Statistical analysis title	NICCE analysis

Statistical analysis description:

Responder analysis with success assigned as patients meeting all the 5 components of the composite endpoint and failure assigned as patients not meeting any one or more of the 5 components of the composite endpoint.

Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.18
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	27.6

Notes:

[8] - Study not powered for comparison of reltecimod and placebo groups in patients with shock at baseline

Post-hoc: Day 14 Through Day 90 Mortality

End point title	Day 14 Through Day 90 Mortality

End point description:

Cumulative mortality (number of deaths) from Day 14 through Day 90

End point type	Post-hoc

End point timeframe:

90 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118[9]	130		
Units: Patients	7	15		

Notes:

[9] - Reltecimod patients in FAS alive at Day 14

Statistical analyses

Statistical analysis title	Day 14-90 Cumulative Mortality

Statistical analysis description:

Study not powered to perform comparison of Day 14-90 mortality between reltecimod and placebo. Used hazard ratio for comparison.

Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	248
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.21

Post-hoc: Day 0 Through Day 90 Mortality in Patients with Baseline mSOFA >=5

End point title	Day 0 Through Day 90 Mortality in Patients with Baseline mSOFA >=5

End point description:

Cumulative mortality (number of deaths) from Day 0 through Day 90 in patients with baseline mSOFA >=5

End point type	Post-hoc

End point timeframe:

90 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[10]	87[11]		
Units: Patients	14	19		

Notes:

[10] - Reltecimod patients in FAS with mSOFA >=5 at baseline

[11] - Placebo patients in FAS with mSOFA >=5 at baseline

Statistical analyses

Statistical analysis title	Cumulative Mortality Day 0-90
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	165
Analysis specification	Post-hoc
Analysis type	other[12]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.68

Notes:

[12] - Study was not powered to assess Day 0-90 mortality rate comparison between reltecimod and placebo. Provide hazard ratio with 95% CIs.

Post-hoc: Day 14 Through Day 90 Mortality in Patients with Baseline mSOFA >=5

End point title	Day 14 Through Day 90 Mortality in Patients with Baseline mSOFA >=5
End point description:	
Cumulative mortality (number of deaths) from Day 14 to Day 90 in patients with baseline mSOFA >=5	
End point type	Post-hoc
End point timeframe:	
90 days	

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66[13]	77[14]		
Units: Patients	2	9		

Notes:

[13] - Reltecimod patients in FAS with mSOFA >=5 at baseline and alive at Day 14

[14] - Placebo patients in FAS with mSOFA >=5 at baseline and alive at Day 14

Statistical analyses

Statistical analysis title	Cumulative Mortality Day 14-90
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	143
Analysis specification	Post-hoc
Analysis type	other[15]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	1.15

Notes:

[15] - Study was not powered to assess Day 14-90 mortality rate comparison between reltecimod and placebo. Provide hazard ratio with 95% CIs.

Post-hoc: Day 14 mSOFA <=1 in Patients with Baseline mSOFA >=5

End point title	Day 14 mSOFA <=1 in Patients with Baseline mSOFA >=5
End point description:	
Patients achieving resolution of organ dysfunction at Day 14, defined as mSOFA score <=1	
End point type	Post-hoc
End point timeframe:	
14 days	

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[16]	87[17]		
Units: Patients	47	36		

Notes:

[16] - Reltecimod patients in FAS with mSOFA >=5 at baseline

[17] - Placebo patients in FAS with mSOFA >=5 at baseline

Statistical analyses

Statistical analysis title	Day 14 mSOFA <=1
Statistical analysis description:	
Responder analysis comparing number of patients achieving Day 14 mSOFA <=1 in reltecimod group vs placebo group	
Comparison groups	Full Analysis Set (FAS)-Placebo v Full Analysis Set (FAS)-Reltecimod
Number of subjects included in analysis	165
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.015
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	33.9

Post-hoc: Day 14 mSOFA <=1 in Patients with Shock at Baseline

End point title	Day 14 mSOFA <=1 in Patients with Shock at Baseline
End point description:	
Patients achieving resolution of organ dysfunction at Day 14, defined as mSOFA <=1.	
End point type	Post-hoc

End point timeframe:

14 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[18]	62[19]		
Units: Patients	51	27		

Notes:

[18] - Reltecimod patients in FAS with shock at baseline

[19] - Placebo patient in FAS with mSOFA >=5 at baseline

Statistical analyses

Statistical analysis title	Day 14 mSOFA <=1
Statistical analysis description:	
Responder analysis comparing number of patients achieving Day 14 mSOFA <=1 in reltecimod group vs placebo group	
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	142
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.016
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	20.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	36.4

Post-hoc: Day 0 Through Day 90 Mortality Among Patients with Shock at Baseline

End point title	Day 0 Through Day 90 Mortality Among Patients with Shock at Baseline
End point description:	
Cumulative mortality (number of deaths) occurring from Day 0 through Day 90	
End point type	Post-hoc
End point timeframe:	
90 days	

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[20]	62[21]		
Units: Patients	14	15		

Notes:

[20] - Reltecimod patients in FAS with shock at baseline

[21] - Placebo patients in FAS with shock at baseline

Statistical analyses

Statistical analysis title	Cumulative Mortality Day 0-90
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-Placebo
Number of subjects included in analysis	142
Analysis specification	Post-hoc
Analysis type	other[22]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.52

Notes:

[22] - Study was not powered to assess Day 0-90 mortality rate comparison between reltecimod and placebo. Provide hazard ratio with 95% CIs.

Post-hoc: Day 14 Through Day 90 Mortality Among Patients with Shock at Baseline

End point title	Day 14 Through Day 90 Mortality Among Patients with Shock at Baseline

End point description:

End point type	Post-hoc

End point timeframe:

90 days

End point values	Full Analysis Set (FAS)-Reltecimod	Full Analysis Set (FAS)-Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[23]	54[24]		
Units: Patients	2	7		

Notes:

[23] - Reltecimod patients in FAS with shock at baseline and alive at Day 14

[24] - Placebo patients in FAS with shock at baseline and alive at Day 14

Statistical analyses

Statistical analysis title	Cumulative Mortality Day 14-90
Comparison groups	Full Analysis Set (FAS)-Reltecimod v Full Analysis Set (FAS)-

	Placebo
Number of subjects included in analysis	122
Analysis specification	Post-hoc
Analysis type	other[25]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	1.04

Notes:

[25] - Study was not powered to assess Day 0-90 mortality rate comparison between reltecimod and placebo. Provide hazard ratio with 95% CIs.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data were collected on Study Days 1, 2, 3, 7, 10, 14, 21, and 28 and via spontaneous reporting. Data associated with deaths and study drug-related serious adverse events (SAEs) were collected though the Day 90 visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Reltecimod 0.5 mg/kg (As Treated)
Reporting group description: -	
Reporting group title	Placebo (As Treated)

Reporting group description: -

Serious adverse events	Reltecimod 0.5 mg/kg (As Treated)	Placebo (As Treated)	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 143 (30.77%)	40 / 147 (27.21%)	
number of deaths (all causes)	24	29	
number of deaths resulting from adverse events	21	24	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 143 (0.70%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant hypertension			

subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Organ failure			
subjects affected / exposed	2 / 143 (1.40%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			

subjects affected / exposed	2 / 143 (1.40%)	4 / 147 (2.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopleural fistula			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 143 (1.40%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 143 (1.40%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 143 (1.40%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 143 (2.80%)	4 / 147 (2.72%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 3	

Cardio-respiratory arrest			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery perforation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary valve incompetence			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulseless electrical activity			
subjects affected / exposed	3 / 143 (2.10%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal compartment syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 143 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal infarction			

subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 143 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver disorder			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin discolouration			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 143 (2.80%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Funguria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Necrotising fasciitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Necrotising soft tissue infection			
subjects affected / exposed	3 / 143 (2.10%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Pneumonia			
subjects affected / exposed	3 / 143 (2.10%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	1 / 143 (0.70%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	3 / 143 (2.10%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Wound infection			
subjects affected / exposed	2 / 143 (1.40%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hyperkalaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Reltecimod 0.5 mg/kg (As Treated)	Placebo (As Treated)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 143 (18.18%)	33 / 147 (22.45%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 143 (4.90%)	8 / 147 (5.44%)	
occurrences (all)	7	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 143 (5.59%)	6 / 147 (4.08%)	
occurrences (all)	10	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 143 (4.20%)	8 / 147 (5.44%)	
occurrences (all)	6	8	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 143 (3.50%)	11 / 147 (7.48%)	
occurrences (all)	5	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2016	Primary revisions include the following: * Change of weight to BMI for exclusion criterion #1. * Addition of Observational Sub-Study of Pre-operative mSOFA = 2 which increases to mSOFA ≥ 3 Postoperatively: The addition of the sub-study for patients with mSOFA = 2 pre-operatively is to assess the percentage of patients who achieve mSOFA ≥ 3 post-operatively but still within 6 hours from the clinical diagnosis (the decision at the study site, to have an urgent surgical exploration and debridement). This sub-study is only for data collection, not intervention. These subjects will still be considered screen failures and will not be randomized to receive blinded study drug. Data will be collected at screening (both pre and postoperatively), day 7 or 10, day 14 and day 29. NICCE outcome will be evaluated to assess comparability to patients with mSOFA ≥ 3 pre-operatively. There have been 55 patients captured on the pre-screening logs with mSOFA = 2 over 8-9 months of study. If the patients are comparable from the sub-study, then there would be consideration for adding this patient group to those eligible to be randomized into the Phase 3 trial, which could increase study accrual by 30-40 patients per year. Since the sub-study is observational, it will not affect the efficacy population nor the endpoints. Inclusion criteria 3 [mSOFA score ≥3 (in any one or combination of the 5 major components of SOFA score with one organ component having a score of at least 2: cardiovascular, respiratory, renal, coagulation, CNS), measured as close as possible to the first debridement, (but before first debridement is performed)] is not changing. As such patients from this observational cohort will still be considered to be screen failures and not be included in the safety or efficacy analysis since the MITT population for this trial only includes patients who are randomized and treated with blinded study drug.
23 August 2018	Primary revisions include the following: * Addition of serum samples for immunogenicity testing: Meet regulatory guidance for immunogenicity testing for peptide molecules. *Study Drug Administration: Added study drug may be manually pushed if approved by the medical monitor, in addition to study drug being administered using a syringe pump. For previous studies with AB103, medical monitor has provided Notes to File to manually push study drug if syringe pump is unavailable or has a malfunction. * Addition of study sites in France: Added sites in France to enhance study enrollment and include EU patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32657946

http://www.ncbi.nlm.nih.gov/pubmed/33797490