Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of a Single Dose of ASN100 for the Prevention of Staphylococcus aureus Pneumonia in Heavily Colonized, Mechanically Ventilated Subjects

Summary

EudraCT number	2016-002146-23
Trial protocol	HU CZ DE ES PT AT PL IT RO
Global end of trial date	28 September 2018

Results information

Result version number	v1 (current)
This version publication date	03 December 2019
First version publication date	03 December 2019

Trial information

Trial identification

Sponsor protocol code	ASN100-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02940626
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Arsanis, Inc.
Sponsor organisation address	890 Winter Street, Waltham, MA, United States, 02451
Public contact	Vice President, Clinical Operations, X4 Pharmaceuticals, Inc. (merged with Arsanis, Inc.), 1 857-529-8300, rnd@x4pharma.com
Scientific contact	Vice President, Clinical Operations, X4 Pharmaceuticals, Inc. (merged with Arsanis, Inc.), 1 857-529-8300, rnd@x4pharma.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 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2018
Global end of trial reached?	Yes
Global end of trial date	28 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of a single dose of ASN100 (administered as ASN-1 and ASN-2 components) versus placebo for the prevention of S. aureus pneumonia in mechanically ventilated subjects who are heavily colonized with S. aureus.

Primary endpoint: Percentage of subjects in the MITT population who have or have not developed S. aureus (SA) pneumonia after a single intravenous (IV) dose of ASN100, based on sponsor defined outcome (SDO1). For each arm, the empirical proportion is defined by a ratio, which is the number of SA pneumonia events divided by the total number of subjects in the arm. The inference about the difference of two population rates is based on the empirical counterpart; specifically, the point estimate, 95% confidence interval and p-value for the rate difference. Subjects discontinued from the study due to any cause prior to Day 22 were considered as not developing SA pneumonia for the primary efficacy analysis.

Protection of trial subjects:

No specific measures in place

Background therapy:

No background therapy

Evidence for comparator:

No comparator, placebo-controlled study design

Actual start date of recruitment	28 November 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	Poland: 9
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Georgia: 65
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Serbia: 3

Country: Number of subjects enrolled	Israel: 4
Worldwide total number of subjects	155
EEA total number of subjects	18

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)	85
From 65 to 84 years	62
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Subjects were randomized at 35 centers in the United States, Austria, Czechia, France, India, Israel, Poland, Portugal, Romania, Serbia, Spain, Republic of Georgia, and Russian Federation

Pre-assignment

Screening details:

Eligible subjects underwent daily screening of endotracheal aspirates to determine if they met randomization criteria. Only randomized are included in the study analysis and summarized in the Participant Flow.
A single subject was randomized in a site-specific pneumonia treatment sub-study and not included in the main study reporting (baseline).

Period 1

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

Blinding implementation details:

Active and placebo vials had identical appearance
No unblinded site personnel, pharmacist also blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ASN100

Arm description:

ASN100 administered as 2 separate intravenous (IV) infusions
ASN100 3600 mg: monoclonal antibody combination of ASN-1 (1800 mg) and ASN-2 (1800 mg) [administered once]

Arm type	Experimental
Investigational medicinal product name	ASN100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single-dose administration
ASN-1 and ASN-2 monoclonal antibody components provided in separate vials
Sequential or simultaneous administration

Arm title	Placebo

Arm description:

Placebo administered as 2 separate intravenous (IV) infusions
Placebo: Placebo [administered once]

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

Dosage and administration details:

Single-dose administration
ASN-1 and ASN-2 placebos provided in separate vials

Sequential or simultaneous administration

Number of subjects in period 1[1]	ASN100	Placebo
Started	77	77
Completed	30	42
Not completed	47	35
Consent withdrawn by subject	1	-
Death	40	32
Transfer to hospice care	1	-
Received prohibitied concomitant medication	-	1
Lost to follow-up	5	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A single subject was randomized in a site-specific pneumonia treatment sub-study and not included in the reporting for the main, prevention study (baseline period).

Baseline characteristics

Reporting groups	
Reporting group title	ASN100
Reporting group description:	
ASN100 administered as 2 separate intravenous (IV) infusions ASN100 3600 mg: monoclonal antibody combination of ASN-1 (1800 mg) and ASN-2 (1800 mg) [administered once]	
Reporting group title	Placebo
Reporting group description:	
Placebo administered as 2 separate intravenous (IV) infusions Placebo: Placebo [administered once]	

Reporting group values	ASN100	Placebo	Total
Number of subjects	77	77	154
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	44	85
From 65-84 years	31	30	61
85 years and over	5	3	8
Age continuous			
Units: years			
arithmetic mean	62.6	59.0	
standard deviation	± 16.97	± 17.44	-
Gender categorical			
Units: Subjects			
Female	27	26	53
Male	50	51	101
Ethnicity			
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	71	71	142
Not reported	2	3	5
Uknown	2	0	2
Race			
Race of subject			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Black or African American	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0

White	71	75	146
Other	4	0	4

End points

End points reporting groups

Reporting group title	ASN100
Reporting group description:	
ASN100 administered as 2 separate intravenous (IV) infusions ASN100 3600 mg: monoclonal antibody combination of ASN-1 (1800 mg) and ASN-2 (1800 mg) [administered once]	
Reporting group title	Placebo
Reporting group description:	
Placebo administered as 2 separate intravenous (IV) infusions Placebo: Placebo [administered once]	

Primary: Efficacy of a Single Intravenous (IV) Dose of ASN100

End point title	Efficacy of a Single Intravenous (IV) Dose of ASN100
End point description:	
Percentage of subjects in the MITT population who have or have not developed S. aureus (SA) pneumonia after a single intravenous (IV) dose of ASN100, based on sponsor defined outcome (SDO1). For each arm, the empirical proportion is defined by a ratio, which is the number of SA pneumonia events divided by the total number of subjects in the arm. The inference about the difference of two population rates is based on the empirical counterpart; specifically, the point estimate, 95% confidence interval and p-value for the rate difference. Subjects discontinued from the study due to any cause prior to Day 22 were considered as not developing SA pneumonia for the primary efficacy analysis.	
End point type	Primary
End point timeframe:	
Up to but no including 22 days post-dosing	

End point values	ASN100	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	76		
Units: Number of subjects				
Developed S. aureus Pneumonia	5	7		
Did Not Develop S. aureus Pneumonia	42	48		
Censored	20	17		
Indeterminate	9	4		

Statistical analyses

Statistical analysis title	Group comparison for S. aureus pneumonia
Statistical analysis description:	
Subjects were analyzed for efficacy in the group to which they randomized. Sponsor defined outcomes were based on review of microbiology results from samples tested at the central lab. If sample was not sent to the central lab, determination was based on results from the local microbiology lab. In cases where both local & central lab results were available, concordance was confirmed for S. aureus. Therefore, the analysis used local microbiology data in order to utilize a more complete dataset.	
Comparison groups	ASN100 v Placebo

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.547
Method	Wald Test on equality of proportions

Notes:

[1] - Wald Test on equality of proportions

Secondary: Duration of Mechanical Ventilation

End point title	Duration of Mechanical Ventilation

End point description:

Duration of mechanical ventilation during the first 21 days post-randomization for subjects in the Modified Intent-to-Treat (MITT) Population

End point type	Secondary

End point timeframe:

21 days

End point values	ASN100	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	71		
Units: days				
arithmetic mean (standard deviation)	11.6 (± 7.47)	10.1 (± 6.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of ICU Stay

End point title	Length of ICU Stay

End point description:

Total length of ICU stay during the first 21 days post-randomization for subjects in the MITT Population

End point type	Secondary

End point timeframe:

Until day 21

End point values	ASN100	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	75		
Units: days				
arithmetic mean (standard deviation)	13.7 (± 6.69)	13.6 (± 7.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: 28-day All-cause Mortality

End point title	28-day All-cause Mortality

End point description:

28-day all-cause mortality in the MITT Population

End point type	Secondary

End point timeframe:

28 days

End point values	ASN100	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	76		
Units: Subjects	30	25		

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-1 Maximum Serum Concentration (Cmax)

End point title	ASN-1 Maximum Serum Concentration (Cmax)[2]

End point description:

The levels of ASN-1 was measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 (final study visit) in subjects who are hospitalized or are able to return to the clinic for blood sampling.

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)	414.43 (± 125.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-2 Maximum Serum Concentration (Cmax)

End point title	ASN-2 Maximum Serum Concentration (Cmax)[3]

End point description:

The levels of ASN-2 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 (final study visit) in subjects who are hospitalized or are able to return to the clinic for blood sampling.

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)	460.88 (± 149.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-1 Time to Maximum Concentration (Tmax) in Serum

End point title	ASN-1 Time to Maximum Concentration (Tmax) in Serum[4]

End point description:

The levels of ASN-1 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: hour				
arithmetic mean (standard deviation)	6.34 (± 10.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-2 Time to Maximum Concentration (Tmax) in Serum

End point title	ASN-2 Time to Maximum Concentration (Tmax) in Serum[5]

End point description:

The levels of ASN-2 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: hour				
arithmetic mean (standard deviation)	4.52 (± 5.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-1 Area Under the Concentration-time Curve in Serum

End point title	ASN-1 Area Under the Concentration-time Curve in Serum[6]

End point description:

The levels of ASN-1 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: µg*h/mL				
arithmetic mean (standard deviation)	44192.3 (± 25080.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-2 Area Under the Concentration-time Curve in Serum

End point title	ASN-2 Area Under the Concentration-time Curve in Serum[7]

End point description:

The levels of ASN-2 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: µg*h/mL				
arithmetic mean (standard deviation)	49366.7 (± 29337.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-1 Terminal Elimination Half-life (t1/2) in Serum

End point title	ASN-1 Terminal Elimination Half-life (t1/2) in Serum[8]

End point description:

The levels of ASN-1 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	54[9]			
Units: hour				
arithmetic mean (standard deviation)	178.9 (± 101.13)			

Notes:

[9] - Only subjects with sufficient number of PK sampling time points analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: ASN-2 Terminal Elimination Half-life (t1/2) in Serum

End point title	ASN-2 Terminal Elimination Half-life (t1/2) in Serum[10]

End point description:

The levels of ASN-2 were measured at completion of study medication infusion, and at 6 hr, 24 hr, Day 4, Day 7, Day 14, Day 22, and Day 90 after completion

End point type	Secondary

End point timeframe:

Through day 90

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ASN-1 and ASN-2 PK parameters are only reported for subjects receiving active ASN100 (i. e. ASN-1 + ASN-2 administered simultaneously or sequentially), as subjects receiving placebo do not have measurable ASN-1 and ASN-2 concentrations.

End point values	ASN100			
Subject group type	Reporting group			
Number of subjects analysed	58[11]			
Units: hour				
arithmetic mean (standard deviation)	185.1 (± 136.09)			

Notes:

[11] - Only subjects with sufficient number of PK sampling time points analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 months. Adverse events (AEs) analyzed include treatment-emergent AEs, from the time of randomization through the Day 90 study visit (i.e. last study visit).

Adverse event reporting additional description:

Only study procedure related AEs were to be reported from the time that informed consent was signed up to randomization, if they were considered to be study procedure related, however no such AEs were reported. Therefore, study procedure related AEs prior to randomization were not analyzed or reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	ASN100

Reporting group description:

ASN100 administered as 2 separate intravenous (IV) infusions
ASN100 3600 mg: monoclonal antibody combination of ASN-1(1800 mg) and ASN-2(1800 mg) [administered once]

Reporting group title	Placebo

Reporting group description:

Placebo administered as 2 separate intravenous (IV) infusions
Placebo: Placebo [administered once]

Serious adverse events	ASN100	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 77 (63.64%)	38 / 77 (49.35%)	
number of deaths (all causes)	41	32	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 77 (2.60%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Shock			

subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurogenic shock			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 77 (1.30%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Death			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 77 (3.90%)	6 / 77 (7.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 5	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tracheal stenosis			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (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	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Craniocerebral injury			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Spinal shock			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	5 / 77 (6.49%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 1	
Cardiac failure acute			
subjects affected / exposed	2 / 77 (2.60%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Ventricular fibrillation			
subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Ventricular asystole			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Bradycardia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial haemorrhage			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular rupture			

subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral congestion			
subjects affected / exposed	6 / 77 (7.79%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 6	0 / 3	
Brain oedema			
subjects affected / exposed	3 / 77 (3.90%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 4	
Coma			
subjects affected / exposed	3 / 77 (3.90%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ischaemic stroke			
subjects affected / exposed	3 / 77 (3.90%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Haemorrhagic transformation stroke			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrospinal fluid circulation disorder			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Guillain-Barre syndrome			

subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Cirrhosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Infections and infestations			
Septic shock			
subjects affected / exposed	3 / 77 (3.90%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Pneumonia	Additional description: Pneumonia, which was an endpoint for the trial, was only entered as an Adverse Event (AE) if it met serious reporting criteria (i.e. SAE)		
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Splenic abscess			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
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	ASN100	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	74 / 77 (96.10%)	69 / 77 (89.61%)	
Congenital, familial and genetic disorders Tracheo-oesophageal fistula subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	4 / 77 (5.19%) 4	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	18 / 77 (23.38%) 18	17 / 77 (22.08%) 19	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	6 / 77 (7.79%) 6 5 / 77 (6.49%) 5	4 / 77 (5.19%) 4 5 / 77 (6.49%) 6	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	15 / 77 (19.48%) 17 5 / 77 (6.49%) 5	11 / 77 (14.29%) 11 2 / 77 (2.60%) 2	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	17 / 77 (22.08%) 25	8 / 77 (10.39%) 12	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	3 / 77 (3.90%)	4 / 77 (5.19%)	
occurrences (all)	3	4	
Diarrhoea			
subjects affected / exposed	8 / 77 (10.39%)	5 / 77 (6.49%)	
occurrences (all)	8	7	
Respiratory, thoracic and mediastinal disorders			
Hydrothorax			
subjects affected / exposed	6 / 77 (7.79%)	3 / 77 (3.90%)	
occurrences (all)	9	3	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	3 / 77 (3.90%)	8 / 77 (10.39%)	
occurrences (all)	4	9	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 77 (10.39%)	5 / 77 (6.49%)	
occurrences (all)	8	5	
Renal failure			
subjects affected / exposed	2 / 77 (2.60%)	4 / 77 (5.19%)	
occurrences (all)	2	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 77 (10.39%)	5 / 77 (6.49%)	
occurrences (all)	8	5	
Bronchitis bacterial			
subjects affected / exposed	16 / 77 (20.78%)	7 / 77 (9.09%)	
occurrences (all)	16	7	
Sinusitis			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	
occurrences (all)	4	2	
Tracheobronchitis			
subjects affected / exposed	5 / 77 (6.49%)	7 / 77 (9.09%)	
occurrences (all)	7	8	
Urinary tract infection			

subjects affected / exposed	16 / 77 (20.78%)	14 / 77 (18.18%)	
occurrences (all)	16	14	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 77 (6.49%)	4 / 77 (5.19%)	
occurrences (all)	5	4	
Hyperkalaemia			
subjects affected / exposed	7 / 77 (9.09%)	6 / 77 (7.79%)	
occurrences (all)	9	7	
Hypernatraemia			
subjects affected / exposed	5 / 77 (6.49%)	3 / 77 (3.90%)	
occurrences (all)	5	4	
Hypoalbuminaemia			
subjects affected / exposed	8 / 77 (10.39%)	2 / 77 (2.60%)	
occurrences (all)	8	2	
Hypocalcaemia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	
occurrences (all)	4	1	
Hypokalaemia			
subjects affected / exposed	9 / 77 (11.69%)	6 / 77 (7.79%)	
occurrences (all)	10	13	
Metabolic acidosis			
subjects affected / exposed	8 / 77 (10.39%)	3 / 77 (3.90%)	
occurrences (all)	9	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2016	Revision of inclusion / exclusion criteria Addition of new exclusion criterion for patients with previous diagnosis of cytokine release syndrome Changes in clinical and microbiological assessments Change in statistical analysis / in adjustment for multiplicity procedures Clarification of sequential or simultaneous administration instructions, specification of time windows for IP administration in both cases Revision of excluded medications / any immunoglobulin preparation for any medical indication is prohibited through follow-up Day 90 of the study
02 May 2017	Revision of study definition of heavy S. aureus colonization to allow qualitative cultures ("For the purposes of this study, heavy colonization of S. aureus will be defined as a quantitative threshold of ≥10e5 CFU/mL or 3+ to 4+ by semi-quantitative culture from an endotracheal aspirate.") Revision of inclusion/exclusion criteria and minor adjustment of study endpoints Addition of subject enrollment option based on independent physicians' review, applicable in coutries where local legislation allows this, to harmonize global protocol with local versions Clarification and revision of randomization criteria Addition of nasal swab sampling at randomization Updates to clinical, laboratory and microbiology assessments Changes and clarifications related to the BAL PK sub-study , 25 to 35 subjects will be invited to participate in this sub-study, involving BAL sampling for PK analysis at 48 hrs post dosing (+/-36 hrs) Revision of pneumonia definition as study endpoint Addition of interim analysis after 125 patients completing follow-up Clarifications, Consistency, Update to chest x-ray / CT Scan requirements to allow standard of care imaging as specifiedűú Clarifications regarding imaging requirements during all phases of the study
23 April 2018	Site-specific amendment to allow randomization of subjects with S. aureus VAP diagnosis into a treatment sub-study Added description of VAP treatment sub-study purpose, rationale and analysis Revised study objectives, inclusion/exclusion and randomization criteria; study procedures updated to reflect the inclusion of subjects into a VAP treatment sub-study Updates in assessments, clinical and microbiological outcome determination and statistical analysis to reflect the inclusion of subjects with VAP diagnosis Related updates to schedule of assessment table

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

An interim analysis of 118 subjects was performed by a DRC to assess S. aureus pneumonia rates and the conditional power to detect a statistically significant treatment effect at study completion (354 subjects). The study was terminated for futility.

Notes: