Clinical trial results:
Placebo-controlled, double-blind, randomized study of Aerucin® as adjunct therapy to antibiotics in the treatment of P. aeruginosa pneumonia

Summary

EudraCT number	2016-004261-10
Trial protocol	BE DE CZ HU ES GR PL IT
Global end of trial date	25 April 2019

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021

Trial information

Trial identification

Sponsor protocol code	AR-105-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03027609
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aridis Pharmaceuticals, Inc.
Sponsor organisation address	983 University Avenue, Building B, Los Gatos, United States, CA 95032-7637
Public contact	Lynne Deans, Vice President (Clinical Development), Aridis Pharmaceuticals, Inc., +1 408385 1742, deansl@aridispharma.com
Scientific contact	Hasan S. Jafri, Chief Medical Officer, Aridis Pharmaceuticals, Inc., +1 408385 1742, jafrih@aridispharma.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	18 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2019
Global end of trial reached?	Yes
Global end of trial date	25 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy of Aerucin®, administered as a single dose in addition to standard antibiotic regimen, in terms of clinical cure at day 14, i.e., resolution of the P. aeruginosa pneumonia event diagnosed at enrollment, as compared to standard antibiotic therapy alone.
2. To assess the clinical safety and tolerability of Aerucin® in the study population.

Protection of trial subjects:

All subjects are hospitalized and monitored for vital function and safety.

Background therapy:

Standard of care antibiotics for bacterial pneumonia

Evidence for comparator: -

Actual start date of recruitment	28 February 2017
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	Spain: 7
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 2
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Belarus: 12
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Ukraine: 17
Worldwide total number of subjects	158
EEA total number of subjects	72

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)	79
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with a documented diagnosis of pneumonia, who are requiring ICU care and who are intubated are eligible for screening. Assuming all other eligibility criteria are met, randomization and treatment will be based on identifying P. Aeruginosa as pathogen causing pneumonia.

Pre-assignment

Screening details:

Screening is divided in two parts. The first part is the pre-screening phase, all subjects with a pneumonia, who are intubated, treated on the ICU and who have a signed Informed consent can move to the second part of screening. In this phase an airway sample (BAL, mini-BAL or ETA) is obtained and sent to the Microbiology Lab or a rapid test is bein

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Drug

Arm description:

AR-105

Arm type	Experimental
Investigational medicinal product name	AR-105
Investigational medicinal product code	AR-105
Other name	Aerucin
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

20 mg/kg via intravenous infusion lasting 2 hours

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

Same volume as AR-105 by intravenous infusion lasting 2 hours

Number of subjects in period 1	Study Drug	Placebo
Started	79	79
Completed	79	79

Baseline characteristics

Reporting groups	
Reporting group title	Study Drug
Reporting group description:	
AR-105	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	Study Drug	Placebo	Total
Number of subjects	79	79	158
Age categorical			
Units: Subjects			
Adults (18-64 years)	40	39	79
Elderly (>65 years)	39	40	79
Age continuous			
Units: years			
arithmetic mean	63.5	61.2	
standard deviation	± 13.83	± 15.58	-
Gender categorical			
Units: Subjects			
Female	17	21	38
Male	62	58	120
Race			
People belonging to different races			
Units: Subjects			
Asian	4	4	8
Black or African American	2	1	3
White	73	74	147
Region of Enrollment			
Regions of Countries from Locations in Protocol			
Units: Subjects			
Americas	3	4	7
Eastern EU	50	50	100
Western EU	22	22	44
Asia	4	3	7

Subject analysis sets	
Subject analysis set title	AR-105
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received study drug	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received study drug (placebo)	
Subject analysis set title	Subset AR-105 Study1

Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of 9 patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

Subject analysis set title	Subset Placebo Study1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of 9 patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

Subject analysis set title	Subset AR-105 Study2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of 9 patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

Subject analysis set title	Subset Placebo Study2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of 9 patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

Reporting group values	AR-105	Placebo	Subset AR-105 Study1
Number of subjects	79	79	9
Age categorical Units: Subjects			
Adults (18-64 years)	40	39	
Elderly (>65 years)	39	40	
Age continuous Units: years			
arithmetic mean	63.5	61.2	
standard deviation	± 13.83	± 15.58	±
Gender categorical Units: Subjects			
Female	17	21	
Male	62	58	
Race			
People belonging to different races			
Units: Subjects			
Asian	4	4	
Black or African American	2	1	
White	73	74	
Region of Enrollment			
Regions of Countries from Locations in Protocol			
Units: Subjects			
Americas	3	4	
Eastern EU	50	50	
Western EU	22	22	

Asia	4	3	

Reporting group values	Subset Placebo Study1	Subset AR-105 Study2	Subset Placebo Study2
Number of subjects	18	3	7
Age categorical Units: Subjects			
Adults (18-64 years) Elderly (>65 years)			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Race			
People belonging to different races			
Units: Subjects			
Asian Black or African American White			
Region of Enrollment			
Regions of Countries from Locations in Protocol			
Units: Subjects			
Americas Eastern EU Western EU Asia			

End points

End points reporting groups

Reporting group title	Study Drug
Reporting group description: AR-105	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	AR-105
Subject analysis set type	Safety analysis
Subject analysis set description: All randomized patients who received study drug	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: All randomized patients who received study drug (placebo)	
Subject analysis set title	Subset AR-105 Study1
Subject analysis set type	Sub-group analysis
Subject analysis set description: A subset of 9 patients had the following characteristics and were found to belong to 1. appropriate clinical Severity 2. inadequate antibiotic regimen and 3. lower 3rd quartile of level of CRP	
Subject analysis set title	Subset Placebo Study1
Subject analysis set type	Sub-group analysis
Subject analysis set description: A subset of 9 patients had the following characteristics and were found to belong to 1. appropriate clinical Severity 2. inadequate antibiotic regimen and 3. lower 3rd quartile of level of CRP	
Subject analysis set title	Subset AR-105 Study2
Subject analysis set type	Sub-group analysis
Subject analysis set description: A subset of 9 patients had the following characteristics and were found to belong to 1. appropriate clinical Severity 2. inadequate antibiotic regimen and 3. lower 3rd quartile of level of CRP	
Subject analysis set title	Subset Placebo Study2
Subject analysis set type	Sub-group analysis
Subject analysis set description: A subset of 9 patients had the following characteristics and were found to belong to 1. appropriate clinical Severity 2. inadequate antibiotic regimen and 3. lower 3rd quartile of level of CRP	

Primary: Clinical Cure on Day 21

End point title	Clinical Cure on Day 21
End point description: A summary of the number (%) of patients who were cured on or before Day 21 (micro-ITT population) is provided, by treatment group	
End point type	Primary
End point timeframe: Up to Day 21	

End point values	AR-105	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	67		
Units: patients				
Observed Cured	34	37		
Imputed Cured	6	5		
Not Cured	25	20		
Reinfection same pathogen	5	2		
New Infection Different Pathogen	0	3		
New infection Unknown pathogen	0	0		

Statistical analyses

Statistical analysis title	CMH Test Day 21 Clinical Cure
Statistical analysis description: Comparison between the treatment and placebo	
Comparison groups	AR-105 v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.6154 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-5.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.9
upper limit	10.8

Notes:

[1] - comparison between the treatment and placebo

[2] - P-value was obtained with the stratified CMH test adjusted for baseline randomization strata

Secondary: Clinical Cure on Day 7

End point title	Clinical Cure on Day 7
End point description: The proportion of patients who achieved Clinical Cure at Day 7	
End point type	Secondary
End point timeframe: Up to Day 7	

End point values	AR-105	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	67		
Units: patients				
Cured Observed	16	18		
Cured Imputed	0	0		
Not Cured	52	47		
Re-infection Same Pathogen	1	0		
New Infection Different Pathogen	1	1		
New Infection Unknown Pathogen	0	1		

Statistical analyses

Statistical analysis title	Day 7 Clinical Cure CMH
Comparison groups	AR-105 v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.8426 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	4.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.5
upper limit	10.5

Notes:

[3] - Comparison between the treatment and placebo

[4] - P-value was obtained with the stratified CMH test adjusted for baseline randomization strata

Secondary: Clinical Cure on Day 14

End point title	Clinical Cure on Day 14

End point description:

A summary of the number (%) of patients who were cured on or before Day 21 (micro-ITT population) is provided by treatment group

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	AR-105	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	67		
Units: Patients				
Observed Cured	36	31		
Imputed Cured	1	2		

Not Cured	29	30		
Reinfection same pathogen	1	0		
New Infection Different Pathogen	2	4		
New infection Unknown pathogen	1	0		

Statistical analyses

Statistical analysis title	CMH Test Day 14 Clinical Cure
Statistical analysis description:	
Comparison between the treatment and placebo	
Comparison groups	AR-105 v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.3562 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	20.3

Notes:

[5] - comparison between the treatment and placebo

[6] - P-value was obtained with the stratified CMH test adjusted for baseline randomization strata

Secondary: Clinical Cure on Day 28

End point title	Clinical Cure on Day 28
End point description:	
A summary of the number (%) of patients who were cured on or before Day 28 (micro-ITT population) is provided by treatment group	
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	AR-105	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	67		
Units: patients				
Observed Cured	35	38		
Imputed Cured	9	6		
Not Cured	23	16		
Reinfection same pathogen	3	3		
New Infection Different Pathogen	0	4		
New infection Unknown pathogen	0	0		

Statistical analyses

Statistical analysis title	CMH Test Day 28 Clinical Cure
Statistical analysis description:	
Comparison between the treatment and placebo	
Comparison groups	AR-105 v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.8472 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	13.2

Notes:

[7] - comparison between the treatment and placebo

[8] - P-value was obtained with the stratified CMH test adjusted for baseline randomization strata

Post-hoc: Post-hoc Analysis of Clinical Cure Rates Day 14 and 21 Study1

End point title	Post-hoc Analysis of Clinical Cure Rates Day 14 and 21 Study1

End point description:

Using the appropriate clinical severity, level of CRP and adequate antibiotic criteria, patients were subdivided into subgroups to identify a pattern in the clinical cure rates in both treatment groups. The results suggest the presence of heterogeneity of factors influencing the clinical cure rates, where only a quite small sample is evaluable.
A subset of patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

End point type	Post-hoc

End point timeframe:

Up to Day 21

End point values	Subset AR-105 Study1	Subset Placebo Study1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	18		
Units: Patients				
Cured Day 14	6	8		
Cured Day 21	7	10		

Statistical analyses

Statistical analysis title	Day 14 Absolute Difference Study1
Statistical analysis description:	
Difference in percentage of clinical cure rates between the two treatment groups	
Comparison groups	Subset AR-105 Study1 v Subset Placebo Study1
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4616 [9]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	22.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	60.6

Notes:

[9] - Marginally statistically significant only if p<0.1
Day 14 p = 0.4616
Day 21 p = 0.4053

Statistical analysis title	Day 21 Absolute Difference Study1
Statistical analysis description:	
Difference in percentage of clinical cure rates between the two treatment groups	
Comparison groups	Subset AR-105 Study1 v Subset Placebo Study1
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4053 [10]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	22.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	57.8

Notes:

[10] - Marginally statistically significant only if p<0.1
Day 21 p = 0.4053

Post-hoc: Post-hoc Analysis of Clinical Cure Rates Day 14 and 21 Study2

End point title	Post-hoc Analysis of Clinical Cure Rates Day 14 and 21 Study2

End point description:

Using the appropriate clinical severity, level of CRP and adequate antibiotic criteria, patients were subdivided into subgroups to identify a pattern in the clinical cure rates in both treatment groups. The results suggest the presence of heterogeneity of factors influencing the clinical cure rates, where only a quite small sample is evaluable.
A subset of patients had the following characteristics and were found to belong to
1. appropriate clinical Severity
2. inadequate antibiotic regimen and
3. lower 3rd quartile of level of CRP

End point type	Post-hoc

End point timeframe:

up to Day 14 and Day 21

End point values	Subset AR-105 Study2	Subset Placebo Study2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	7		
Units: patients				
Cured Day 14	2	2		
Cured Day 21	2	3		

Statistical analyses

Statistical analysis title	Day14 Absolute Difference Study2

Statistical analysis description:

Difference in percentage of clinical cure rates between the two treatment groups

Comparison groups	Subset AR-105 Study2 v Subset Placebo Study2
Number of subjects included in analysis	10
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0833 [11]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	38.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.8
upper limit	90.9

Notes:

[11] - Marginally statistically significant only if p<0.1
Day 14 p = 0.0833

Statistical analysis title	Day21 Absolute Difference Study2

Statistical analysis description:

Difference in percentage of clinical cure rates between the two treatment groups

Comparison groups	Subset AR-105 Study2 v Subset Placebo Study2

Number of subjects included in analysis	10
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5151 [12]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	23.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-30.5
upper limit	78.1

Notes:

[12] - Marginally statistically significant only if p<0.1
Day 21 p = 0.5151

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Day 0 to Day 28	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	AR-105
Reporting group description: The patients that were given study drug AR-105	
Reporting group title	Placebo
Reporting group description: Patients receiving placebo	

Serious adverse events	AR-105	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 79 (45.57%)	22 / 79 (27.85%)	
number of deaths (all causes)	25	13	
number of deaths resulting from adverse events	25	13	
Vascular disorders			
Arterial rupture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			

subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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			
Cardiac death			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	7 / 79 (8.86%)	4 / 79 (5.06%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 3	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
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 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 79 (3.80%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	5 / 79 (6.33%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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	3 / 79 (3.80%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 79 (2.53%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	3 / 79 (3.80%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardio-respiratory arrest			
subjects affected / exposed	1 / 79 (1.27%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 79 (1.27%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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	1 / 79 (1.27%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhythm idioventricular			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	3 / 79 (3.80%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 79 (3.80%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	

Pneumonia bacterial			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 79 (3.80%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	5 / 79 (6.33%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 2	
Systemic candida			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AR-105	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 79 (92.41%)	73 / 79 (92.41%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	14 / 79 (17.72%)	9 / 79 (11.39%)	
occurrences (all)	14	9	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	10 / 79 (12.66%)	4 / 79 (5.06%)	
occurrences (all)	10	4	
Oedema peripheral			
subjects affected / exposed	1 / 79 (1.27%)	4 / 79 (5.06%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	5 / 79 (6.33%)	3 / 79 (3.80%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Hydrothorax			
subjects affected / exposed	5 / 79 (6.33%)	3 / 79 (3.80%)	
occurrences (all)	5	3	
Pneumothorax			
subjects affected / exposed	4 / 79 (5.06%)	2 / 79 (2.53%)	
occurrences (all)	4	2	
Respiratory failure			
subjects affected / exposed	5 / 79 (6.33%)	0 / 79 (0.00%)	
occurrences (all)	5	0	
Tachypnoea			
subjects affected / exposed	4 / 79 (5.06%)	3 / 79 (3.80%)	
occurrences (all)	4	3	
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 79 (5.06%)	2 / 79 (2.53%)	
occurrences (all)	4	2	

Delirium			
subjects affected / exposed	4 / 79 (5.06%)	2 / 79 (2.53%)	
occurrences (all)	4	2	
Insomnia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 79 (3.80%)	
occurrences (all)	4	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 79 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	6	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 79 (0.00%)	6 / 79 (7.59%)	
occurrences (all)	0	6	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 79 (7.59%)	7 / 79 (8.86%)	
occurrences (all)	6	7	
Bradycardia			
subjects affected / exposed	2 / 79 (2.53%)	4 / 79 (5.06%)	
occurrences (all)	2	4	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	5 / 79 (6.33%)	0 / 79 (0.00%)	
occurrences (all)	5	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 79 (20.25%)	13 / 79 (16.46%)	
occurrences (all)	16	13	
Thrombocytopenia			
subjects affected / exposed	6 / 79 (7.59%)	1 / 79 (1.27%)	
occurrences (all)	6	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 79 (7.59%)	2 / 79 (2.53%)	
occurrences (all)	6	2	
Diarrhoea			

subjects affected / exposed	5 / 79 (6.33%)	13 / 79 (16.46%)	
occurrences (all)	5	13	
Nausea			
subjects affected / exposed	3 / 79 (3.80%)	4 / 79 (5.06%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	6 / 79 (7.59%)	9 / 79 (11.39%)	
occurrences (all)	6	9	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 79 (5.06%)	4 / 79 (5.06%)	
occurrences (all)	4	4	
Infections and infestations			
Cystitis			
subjects affected / exposed	4 / 79 (5.06%)	4 / 79 (5.06%)	
occurrences (all)	4	4	
Pneumonia			
subjects affected / exposed	5 / 79 (6.33%)	5 / 79 (6.33%)	
occurrences (all)	5	5	
Sepsis			
subjects affected / exposed	5 / 79 (6.33%)	0 / 79 (0.00%)	
occurrences (all)	5	0	
Septic shock			
subjects affected / exposed	6 / 79 (7.59%)	5 / 79 (6.33%)	
occurrences (all)	6	5	
Tracheobronchitis			
subjects affected / exposed	4 / 79 (5.06%)	2 / 79 (2.53%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	6 / 79 (7.59%)	
occurrences (all)	1	6	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	6 / 79 (7.59%)	4 / 79 (5.06%)	
occurrences (all)	6	4	
Hypernatraemia			

subjects affected / exposed	4 / 79 (5.06%)	1 / 79 (1.27%)	
occurrences (all)	4	1	
Hypokalaemia			
subjects affected / exposed	12 / 79 (15.19%)	6 / 79 (7.59%)	
occurrences (all)	12	6	
Hypovolaemia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 79 (3.80%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2018	This amendment was made in response to further considerations and clarifications of the study design, data integrity, and patient safety. Major updates included, but not limited to: Clarification of clinical cure rates with standard of cure antibiotic regimen Update of rapid diagnostic testing device GeneXpert® PA Cartridge, with addition of CE mark and IUO/RUO Addition of 19 years minimum age for South Korea Addition of third stratification (Country of Origin) Addition of no impact on treatment disclaimer Addition of severity status and biomarker sample tests Removal of time 0 for vital signs control Minor editorial changes, change of relapse to re-infection/new infection, and of VABP with VAP; addition of the terminology 'quantitative/semi quantitative' for culture tests and change of the IMP name to AR-105
09 November 2018	The changes to the protocol were made as a result of the approval of the revised Clinical Cure criteria to be used in a post hoc efficacy assessment by an adjudication committee. The changes included: Section 2: Clarification of Clinical Cure (CC) rates with standard of cure antibiotic regimen in the primary clinical efficacy objective. Removal of Day 4 and reordering of CC rates and removal of adjudication by independent committee in the secondary clinical efficacy objective Section 3.1: Specification of patients with VAP caused by P. aeruginosa; addition of clarification for ETA sample collection, randomization process (including subpopulations with different baseline oxygen status), procedures (CC criteria) used by an adjudication committee (AC), pneumonia causing pathogen and antibiotic treatment limit of 14 days, addition of reference to best practices for the choice of SOC antibiotics. Removal of comparison of culture results between laboratories and assessment of therapy by AC Section 4.3: Removal of withdrawal criteria: occurrence of any medical condition, SAEs, pregnancy, prohibited medication, protocol compliance; addition of loss to follow-up and clarification of study continuation through Day 28 Section 6.5: Removal of reference to AC, additional confirmation of randomization at earliest possible time and nearest specimen collection for microbiological outcome assessment, correction of computation of SOFA scores at set dates Section 7.3: Addition of central laboratory and clarification of 'eradicated' criteria All sections (where applicable): Change of 'relapse' to 're-infection/new infection', and of VABP with VAP; addition of the terminology 'quantitative/semi quantitative' for culture tests and standardization of the font formatting of the ® trademark on the IMP name AR-105

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.

Although the efficacy of AR-105 was not superior to placebo in 159 patients, a post-hoc analysis revealed a numeric difference of over 20% (absolute value) in clinical cure rate in favor of AR-105 in a subgroup of patients.

Notes: