Clinical trial results:
Dose Escalation Part:
MULTIDOSE SAFETY AND TOLERABILITY STUDY OF DOSE ESCALATION OF LIPOSOMAL AMIKACIN FOR INHALATION (ARIKACE™) IN CYSTIC FIBROSIS PATIENTS WITH CHRONIC INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

Extension Part:
MULTIDOSE SAFETY AND TOLERABILITY STUDY OF DOSE ESCALATION OF LIPOSOMAL AMIKACIN FOR INHALATION (ARIKACE™) IN CYSTIC FIBROSIS PATIENTS WITH CHRONIC INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

Summary

EudraCT number	2006-006980-22
Trial protocol	HU SK BE PL
Global end of trial date	02 November 2010

Results information

Result version number	v1 (current)
This version publication date	04 August 2020
First version publication date	04 August 2020

Trial information

Trial identification

Sponsor protocol code	TR02-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00777296
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Insmed Incorporated
Sponsor organisation address	700 US Highway 202/206, Bridgewater, United States, 08807-1704
Public contact	Tom Vanthienen, Insmed Incorporated, +41 795432860, tom.vanthienen@insmed.com
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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	No

1901/2006 apply to this trial?	
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	11 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2008
Global end of trial reached?	Yes
Global end of trial date	02 November 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Dose Escalation Part:
To evaluate the safety and tolerability of 28 days of daily dosing of two dose cohorts of nebulized Arikace™, liposomal amikacin for inhalation.

Extension Part:
To evaluate the longer-term safety, tolerability and efficacy of 560 mg once daily (QD) dose of Arikace™ administered for 6 cycles over 18 months. Each cycle comprised 28 days on treatment followed by 56 days off treatment.

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, the International Council for Harmonisation (ICH) Guidelines, and is consistent with the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2007
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: 18
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 25
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Ukraine: 24
Worldwide total number of subjects	124
EEA total number of subjects	57

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)	27
Adolescents (12-17 years)	46
Adults (18-64 years)	51
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 15 study centres for the Dose Escalation Part of the study, and at 11 study centres for the Extension Part.

Pre-assignment

Screening details:

The 2 cohorts involved in the Dose Escalation Part of the study were randomised to receive Arikace™ or a placebo at a 2:1 ratio. All subjects who progressed into the Extension Part of the study received Arikace™.

Period 1

Period 1 title	TR02-105 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose Escalation Part - Cohort 1 - 280 mg Arikace™

Arm description:

Subjects in this cohort received 280 mg of Arikace™.

Arm type	Experimental
Investigational medicinal product name	Arikace™
Investigational medicinal product code	
Other name	Liposomal amikacin for inhalation
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received a once daily dose of Arikace™ 280 mg for 28 days in Cohort 1. Subjects received a once daily dose of Arikace™ 560 mg for 28 days in Cohort 2. Arikace™ was administered via a PARI eFlow nebulizer over approximately 20 minutes.

Arm title	Dose Escalation Part - Cohort 1 - Placebo

Arm description:

Subjects in this arm of Cohort 1 received matching placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received a once daily dose of the placebo for 28 days in Cohort 1. Subjects received a once daily dose of the placbo for 28 days in Cohort 2. The placebo was administered via a PARI eFlow nebulizer over approximately 20 minutes.

Arm title	Dose Escalation Part - Cohort 2 - 560 mg Arikace™

Arm description:

Subjects in this cohort received 560 mg of Arikace™.

Arm type	Experimental

Investigational medicinal product name	Arikace™
Investigational medicinal product code	
Other name	Liposomal amikacin for inhalation
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received a once daily dose of Arikace™ 280 mg for 28 days in Cohort 1. Subjects received a once daily dose of Arikace™ 560 mg for 28 days in Cohort 2. Arikace™ was administered via a PARI eFlow nebulizer over approximately 20 minutes.

Arm title	Dose Escalation Part - Cohort 2 - Placebo

Arm description:

Subjects in this arm of Cohort 2 received matching placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received a once daily dose of the placebo for 28 days in Cohort 1. Subjects received a once daily dose of the placebo for 28 days in Cohort 2. The placebo was administered via a PARI eFlow nebulizer over approximately 20 minutes.

Arm title	Extension Part

Arm description:

Subjects in the Extension Part received 560 mg of Arikace™.

Arm type	Experimental
Investigational medicinal product name	Arikace™
Investigational medicinal product code	
Other name	Liposomal amikacin inhalation
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

All subjects received a dose of 560 mg of Arikace™ once daily for 28 days. Arikace™ was administered via a PARI eFlow nebulizer over approximately 10 minutes.

Number of subjects in period 1[1]	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Started	21	11	23
Completed	20	10	21
Not completed	1	1	2
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	-
Pregnancy	-	-	-
Completed study but not 24 of 28 days	-	-	-
Case Report Form (CRF) not completed	-	-	2
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	Dose Escalation Part - Cohort 2 - Placebo	Extension Part
Started	11	49
Completed	10	41
Not completed	1	8
Consent withdrawn by subject	-	3
Adverse event, non-fatal	1	1
Pregnancy	-	1
Completed study but not 24 of 28 days	-	2
Case Report Form (CRF) not completed	-	-
Lack of efficacy	-	1

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: Eligible subjects in the Dose Escalation Part of the study moved onto the Extension Part of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Dose Escalation Part - Cohort 1 - 280 mg Arikace™
Reporting group description:	
Subjects in this cohort received 280 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 1 - Placebo
Reporting group description:	
Subjects in this arm of Cohort 1 received matching placebo.	
Reporting group title	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Reporting group description:	
Subjects in this cohort received 560 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 2 - Placebo
Reporting group description:	
Subjects in this arm of Cohort 2 received matching placebo.	
Reporting group title	Extension Part
Reporting group description:	
Subjects in the Extension Part received 560 mg of Arikace™.	

Reporting group values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Number of subjects	21	11	23
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	16.0	16.9	16.6
standard deviation	± 5.3	± 7.9	± 6.1
Gender categorical Units: Subjects			
Female	16	8	11
Male	5	3	12

Reporting group values	Dose Escalation Part - Cohort 2 - Placebo	Extension Part	Total
Number of subjects	11	49	115
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	17.2	17.4	
standard deviation	± 5.8	± 6.22	-
Gender categorical			
Units: Subjects			
Female	4	29	68
Male	7	20	47

End points

End points reporting groups

Reporting group title	Dose Escalation Part - Cohort 1 - 280 mg Arikace™
Reporting group description:	
Subjects in this cohort received 280 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 1 - Placebo
Reporting group description:	
Subjects in this arm of Cohort 1 received matching placebo.	
Reporting group title	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Reporting group description:	
Subjects in this cohort received 560 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 2 - Placebo
Reporting group description:	
Subjects in this arm of Cohort 2 received matching placebo.	
Reporting group title	Extension Part
Reporting group description:	
Subjects in the Extension Part received 560 mg of Arikace™.	
Subject analysis set title	Pooled Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Placebo is a pooled value from cohort 280 mg and cohort 560 mg.	
Subject analysis set title	Arikace™
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects who received either the 280 mg or the 560 mg doses of the Arikace™.	

Primary: Dose Escalation Part: Clinically Significant Laboratory Abnormalities

End point title	Dose Escalation Part: Clinically Significant Laboratory Abnormalities[1][2]
End point description:	
Changes in chemistry and hematology lab tests (clinically significant value of Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
28 Days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not planned for this endpoint.

[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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Dose Escalation Part - Cohort 2 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	21	11
Units: Subjects				
Neutrophils absolute	1	0	8	7
Leucocytes	1	0	3	3
Glucose	0	0	2	0
Lymphocytes absolute	1	0	2	0
Calcium	0	0	1	0
Creatinine clearance	0	0	1	0
Potassium	3	1	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Extension Part: Adverse Event Profile of 560 mg Once Daily Dose of Arikace™ Administered for Six Cycles Over Eighteen Months

End point title	Extension Part: Adverse Event Profile of 560 mg Once Daily Dose of Arikace™ Administered for Six Cycles Over Eighteen Months[3][4]

End point description:

Number of subjects with indicated adverse events in subject receiving 560 mg once daily dose of Arikace™ administered for 6 cycles over 18 months.

End point type	Primary

End point timeframe:

18 Months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

[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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Subjects				
Any Adverse Event	48			
Treatment-related adverse events	15			
Grade 1: Mild	28			
Grade 2: Moderate	15			
Grade 3: Severe	4			
Grade 4: Life-threatening or disabling	1			
Grade 5: Death	0			
Serious Adverse Events	15			

Treatment-related serious adverse events	0			
Deaths	0			
Permanent discontinuations due to adverse events	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Serum

End point title	Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Serum[5]

End point description:

Measure PK parameters (AUC0-infinity) of Arikace™ in serum.

The PK population consisted of subjects who received amikacin, had at least one serum PK assessment and were not replaced.

End point type	Secondary

End point timeframe:

Day 1, Day 14 and Day 28

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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: mg.hr/L				
arithmetic mean (standard deviation)				
Day 1	5.73 (± 3.40)	7.92 (± 3.55)		
Day 14	7.61 (± 4.04)	12.5 (± 10.9)		
Day 28	8.03 (± 6.12)	14.6 (± 11.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetic (PK) of Arikace™ in Serum (Cmax)

End point title	Dose Escalation Part: Pharmacokinetic (PK) of Arikace™ in Serum (Cmax)[6]

End point description:

Measure PK parameter (Cmax) of Arikace™ in serum.

The PK population consisted of subjects who received Arikace™, had at least one serum PK assessment and were not replaced.

End point type	Secondary

End point timeframe:

Day 1, Day 14 and Day 28

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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: mg/L				
arithmetic mean (standard deviation)				
Day 1	0.95 (± 0.58)	1.08 (± 0.51)		
Day 14	1.28 (± 1.02)	1.84 (± 1.35)		
Day 28	1.42 (± 1.45)	2.27 (± 1.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Sputum (AUC)

End point title	Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Sputum (AUC)[7]

End point description:

Measure PK parameter (AUC0-24) of Arikace™ in sputum.

End point type	Secondary

End point timeframe:

28 days

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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: mcg*hr/g				
arithmetic mean (standard deviation)	13120 (± 21386)	22445 (± 18652)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Urine

End point title	Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Urine[8]

End point description:

Measure PK parameter (Ae0-24 ((mg)) of Arikace™.

The PK population consisted of subjects who received amikacin, had at least one serum PK assessment and were not replaced.

End point type	Secondary

End point timeframe:

Day 1, Day 14 and Day 28

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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: mg				
arithmetic mean (standard deviation)				
Day 1	17.7 (± 12.3)	27.0 (± 25.2)		
Day 14	27.3 (± 16.5)	39.8 (± 42.7)		
Day 28	25.2 (± 19.5)	43.7 (± 48.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Sputum Amikacin Levels of Arikace™

End point title	Dose Escalation Part: Sputum Amikacin Levels of Arikace™[9]

End point description:

Measure PK parameter (sputum amicakin concentration) of Arikace™ in sputum.

End point type	Secondary

End point timeframe:

Day 1, Day 14 and Day 28

Notes:

[9] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: mcg/g				
arithmetic mean (standard deviation)				
Day 1	1197 (± 1.56)	2395 (± 0.866)		
Day 14	1174 (± 1.01)	3496 (± 0.973)		
Day 28	1911 (± 1.28)	2635 (± 1.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pulmonary Function: FEV1 %-Predicted

End point title	Dose Escalation Part: Pulmonary Function: FEV1 %-

End point description:

Relative change (%) from baseline to end of treatment (Day 28) and Day 56 in pulmonary function.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 56

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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	21	22	
Units: Relative Percent (%) change in FEV1				
arithmetic mean (standard deviation)				
Baseline	66.4 (± 20.0)	62.9 (± 18.2)	68.0 (± 22.4)	
Day 28	9.6 (± 13.7)	11.0 (± 16.4)	0.5 (± 10.5)	
Day 56	1.8 (± 8.8)	13.8 (± 26.2)	-3.8 (± 13.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pulmonary Function: FEV1

End point title	Dose Escalation Part: Pulmonary Function: FEV1[11]

End point description:

Mean percent change (%) from baseline to end of treatment (Day 28) and Day 56 in pulmonary function.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 56

Notes:

[11] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	21	22	
Units: Mean Percent (%) Change in FEV1				
arithmetic mean (standard deviation)				
Baseline	2.022 (± 0.788)	1.937 (± 0.936)	1.968 (± 0.654)	
Day 28	10.1 (± 12.8)	13.2 (± 16.2)	2.2 (± 11.9)	
Day 56	2.0 (± 8.6)	13.2 (± 24.3)	-4.4 (± 13.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Change From Baseline in Log10CFU Per Gram (Density) of Pseudomonas Aeruginosa in Sputum

End point title	Dose Escalation Part: Change From Baseline in Log10CFU Per Gram (Density) of Pseudomonas Aeruginosa in Sputum[12]

End point description:

End of treatment (Day 28) from baseline in density of P. aeruginosa (log10 CFU/g) in sputum.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Day 7, Day 14, Day 21, Day 28 and Day 35

Notes:

[12] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	21	22	
Units: log10CFU per gram				
arithmetic mean (standard deviation)				
Day 7	0.080 (± 1.882)	-1.101 (± 2.170)	0.052 (± 1.303)	
Day 14	-1.366 (± 2.013)	-1.570 (± 2.161)	-0.574 (± 1.006)	
Day 21	-1.044 (± 2.155)	-2.283 (± 2.775)	-0.440 (± 1.280)	
Day 28	-0.622 (± 1.881)	-1.515 (± 1.699)	-0.677 (± 1.043)	
Day 35	-0.380 (± 1.425)	-1.313 (± 2.852)	-0.445 (± 1.201)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Duration of Systemic Antipseudomonal Rescue Therapy

End point title	Dose Escalation Part: Duration of Systemic Antipseudomonal Rescue Therapy[13]

End point description:

Duration of systemic antipseudomonal rescue therapy during the study in both the Arikace™ and placebo groups.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Through study duration, approximately 56 days

Notes:

[13] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Dose Escalation Part - Cohort 2 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11[14]	21[15]	11
Units: Days				
arithmetic mean (standard deviation)	14.00 (± 0.00)	27.00 (± 99999)	19.00 (± 99999)	21.00 (± 11.31)

Notes:

[14] - 99999 is used where standard deviation doesn't apply as only 1 subject required rescue therapy.

[15] - 99999 is used where standard deviation doesn't apply as only 1 subject required rescue therapy.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Number of Subjects Requiring Antipseudomonal Rescue Therapy

End point title	Dose Escalation Part: Number of Subjects Requiring Antipseudomonal Rescue Therapy

End point description:

Number of subjects requiring systemic antipseudomonal rescue therapy during the study in both the Arikace™ and placebo groups.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Through study duration, approximately 56 days

End point values	Pooled Placebo	Arikace™		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	42		
Units: Subjects	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: CFQ-R Respiratory Scale (Absolute Change From Baseline)

End point title	Dose Escalation Part: CFQ-R Respiratory Scale (Absolute Change From Baseline)[16]

End point description:

Quality of Life was measured by the absolute change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory scale. Disease specific instrument designed to measure impact on overall health, daily life, perceived well-being and symptoms in subjects with a diagnosis of cystic fibrosis. Scores range from 0 to 100, with higher scores indicating better health. Scores for each Health Related Quality of Life (HRQoL) domain; after recoding, each item is summed to generate a domain score and

standardized.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline/Day 1, Day 15, Day 28 and Day 42

Notes:

[16] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™	Dose Escalation Part - Cohort 2 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	21	11
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day 1/Baseline	72.619 (± 11.630)	71.212 (± 14.921)	67.989 (± 12.748)	61.364 (± 21.425)
Day 15	2.632 (± 10.078)	-0.505 (± 12.349)	3.704 (± 16.133)	-2.778 (± 16.054)
Day 28	4.306 (± 12.760)	-3.283 (± 14.154)	5.688 (± 11.669)	1.667 (± 13.302)
Day 42	1.080 (± 12.169)	-4.012 (± 19.598)	3.042 (± 18.213)	0.556 (± 12.200)

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: FEV1 % Predicted

End point title	Extension Part: FEV1 % Predicted[17]

End point description:

A summary of relative change from the Extension Part of the study baseline time points in FEV1 % predicted is presented for the overall safety population and by treatment received.

Safety population.

End point type	Secondary

End point timeframe:

Baseline, Days 1, 14, 28, 56, 70, 85, 98, 112, 140, 154, 169, 182,196, 224, 238, 253, 266, 280, 308, 322, 337, 350, 364, 392, 406, 421, 434, 448, 476, 490 and 504

Notes:

[17] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49[18]			
Units: Percent (%) predicted				
arithmetic mean (standard deviation)				
Baseline	59.73 (± 20.047)			
Day 1	3.13 (± 8.553)			
Day 14	7.62 (± 15.246)			
Day 28	6.83 (± 14.593)			
Day 56	3.02 (± 11.174)			
Day 70	2.96 (± 13.580)			
Day 85	4.04 (± 15.450)			
Day 98	9.97 (± 16.594)			
Day 112	8.19 (± 20.116)			
Day 140	4.86 (± 19.337)			
Day 154	6.76 (± 20.633)			
Day 169	3.90 (± 19.141)			
Day 182	10.22 (± 18.349)			
Day 196	7.56 (± 20.607)			
Day 224	2.57 (± 19.165)			
Day 238	5.46 (± 17.872)			
Day 253	3.37 (± 17.755)			
Day 266	9.07 (± 19.747)			
Day 280	8.54 (± 19.179)			
Day 308	5.77 (± 19.633)			
Day 322	5.25 (± 20.946)			
Day 337	5.18 (± 21.740)			
Day 350	10.49 (± 21.615)			
Day 364	3.82 (± 18.895)			
Day 392	3.07 (± 18.380)			
Day 406	2.74 (± 18.301)			
Day 421	1.63 (± 19.094)			
Day 434	7.11 (± 20.022)			

Day 448	5.66 (± 20.422)			
Day 476	0.83 (± 21.741)			
Day 490	1.61 (± 19.922)			
Day 504	0.06 (± 22.196)			

Notes:

[18] - Number of subjects analysed ranged from 49 to 42.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Absolute Change in Sputum Density

End point title	Extension Part: Absolute Change in Sputum Density[19]

End point description:

A summary of change from the Extension Part baseline to all post-baseline time points during the treatment periods and at the end of the off treatment periods in P aeruginosa sputum density (log10 CFU/mL) is presented for the overall safety population and by treatment received.

Per Protocol population defined as all subjects who completed at least 24 of the 28 days of dosing for each of the 6 cycles

End point type	Secondary

End point timeframe:

Baseline, Days 14, 28, 85, 98, 112, 140, 169, 182,196, 253, 266, 280, 337, 350, 364, 421, 434 and 448

Notes:

[19] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49[20]			
Units: Log 10 CFU/mL				
arithmetic mean (standard deviation)				
Baseline	6.289 (± 2.8587)			
Day 14	-1.196 (± 2.0736)			
Day 28	-0.416 (± 1.8584)			
Day 85	0.154 (± 2.4433)			
Day 98	-0.623 (± 1.9127)			
Day 112	-0.781 (± 1.1625)			
Day 140	-0.266 (± 0.2871)			
Day 169	-0.144 (± 1.2470)			
Day 182	-1.087 (± 1.9582)			

Day 196	-0.599 (± 1.3450)			
Day 253	0.213 (± 1.4059)			
Day 266	-0.991 (± 2.5040)			
Day 280	-0.702 (± 1.7419)			
Day 337	0.375 (± 1.9924)			
Day 350	-0.311 (± 1.6342)			
Day 364	-0.107 (± 1.8027)			
Day 421	0.494 (± 2.0058)			
Day 434	0.111 (± 1.9098)			
Day 448	0.034 (± 2.0020)			

Notes:

[20] - Subjects analysed ranged from 49 to 30.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Antipseudomonal Rescue Therapy - Duration of Therapy

End point title	Extension Part: Antipseudomonal Rescue Therapy - Duration of Therapy[21]

End point description:

The duration of IV and all systemic or inhaled antipseudomonal rescue therapy is presented for the overall safety population and by treatment received.

End point type	Secondary

End point timeframe:

18 Months

Notes:

[21] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
arithmetic mean (standard deviation)	39.7 (± 44.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Antipseudomonal Rescue Therapy - Time to Therapy

End point title	Extension Part: Antipseudomonal Rescue Therapy - Time to Therapy[22]

End point description:

The time to IV and all systemic or inhaled antipseudomonal rescue therapy is presented for the overall safety population and by treatment received.

End point type	Secondary

End point timeframe:

18 Months

Notes:

[22] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage (%) subjects				
number (not applicable)				
By Day 85	2.0			
By Day 253	17.2			
By Day 504	32.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Analysis of Cystic Fibrosis Questionnaire - Revised (CFQ-R) for Absolute Change in Score

End point title	Extension Part: Analysis of Cystic Fibrosis Questionnaire - Revised (CFQ-R) for Absolute Change in Score[23]

End point description:

A summary of absolute change from baseline in the CFQ-R scales at each on treatment assessment between Day 14 and Day 448 is presented for all subjects and by main study treatment group for the safety population. CFQ-R is a disease specific instrument designed to measure impact on overall health, daily life, perceived well-being and symptoms on a scale from 0 to 100 points. Higher values represent a more favorable outcome.

End point type	Secondary

End point timeframe:

Days 14, 28, 85, 98, 112, 169, 182,196, 253, 266, 280, 337, 350, 364, 421, 434 and 448

Notes:

[23] - 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: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

End point values	Extension Part			
Subject group type	Reporting group			
Number of subjects analysed	49[24]			
Units: Percentage (%)				
arithmetic mean (standard deviation)				
Day 14	7.616 (± 14.1662)			
Day 28	11.486 (± 14.9347)			
Day 85	9.697 (± 12.9834)			
Day 98	11.235 (± 14.5552)			
Day 112	11.768 (± 13.9321)			
Day 169	5.159 (± 13.6851)			
Day 182	9.233 (± 16.3635)			
Day 196	9.404 (± 12.4334)			
Day 253	7.097 (± 13.7509)			
Day 266	10.041 (± 14.5240)			
Day 280	6.111 (± 11.3611)			
Day 337	9.017 (± 13.8786)			
Day 350	12.108 (± 13.8668)			
Day 364	11.875 (± 12.9679)			
Day 421	11.895 (± 14.1632)			
Day 434	13.718 (± 13.1377)			
Day 448	13.120 (± 14.0144)			

Notes:

[24] - Subjects analysed ranged from 48 to 39.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Dose Escalation Part:
AEs were assessed from the first dose (Visit 2) until the completion of the study follow-up (14 days after 28 days of dosing in cohort 2). The total duration is approximately 84 days.

Extension Part:
18 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Dose Escalation Part - Cohort 1 - 280 mg Arikace™
Reporting group description:	
Subjects in this cohort received 280 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 1 - Placebo
Reporting group description:	
Subjects in this arm of cohort 1 received matching placebo.	
Reporting group title	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Reporting group description:	
Subjects in this cohort received 560 mg of Arikace™.	
Reporting group title	Dose Escalation Part - Cohort 2 - Placebo
Reporting group description:	
Subjects in this arm of cohort 2 received matching placebo.	
Reporting group title	Extension Part
Reporting group description:	
Subjects in the Extension Part received 560 mg of Arikace™.	

Serious adverse events	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	2 / 21 (9.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Endoscopy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic			

disorders			
Cystic fibrosis lung			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Drug therapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular appendage torsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug abuse			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dose Escalation Part - Cohort 2 - Placebo	Extension Part	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	15 / 49 (30.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Endoscopy			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
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			
Cystic fibrosis lung			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	11 / 49 (22.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Drug therapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular appendage torsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
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			
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug abuse			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
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	Dose Escalation Part - Cohort 1 - 280 mg Arikace™	Dose Escalation Part - Cohort 1 - Placebo	Dose Escalation Part - Cohort 2 - 560 mg Arikace™
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)	6 / 11 (54.55%)	5 / 21 (23.81%)
Investigations			

Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 21 (4.76%)	2 / 11 (18.18%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Aphthous stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Haemoptysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Lung disorder			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 21 (4.76%)	1 / 11 (9.09%)	2 / 21 (9.52%)
occurrences (all)	1	2	2
Productive cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 21 (14.29%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	4	1	0
Rhinitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 11 (9.09%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 21 (4.76%)	1 / 11 (9.09%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 21 (9.52%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 21 (9.52%)	0 / 11 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Dose Escalation Part - Cohort 2 - Placebo	Extension Part	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	29 / 49 (59.18%)	
Investigations			
Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 49 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 49 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	5 / 49 (10.20%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Aphthous stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 49 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	14 / 49 (28.57%)	
occurrences (all)	0	33	
Haemoptysis			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	12 / 49 (24.49%)	
occurrences (all)	0	20	
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Productive cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	11 / 49 (22.45%)	
occurrences (all)	1	14	
Rhinitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	2 / 49 (4.08%)	
occurrences (all)	1	5	
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 49 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	14 / 49 (28.57%)	
occurrences (all)	1	26	
Pharyngitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 11 (0.00%)	5 / 49 (10.20%)	
occurrences (all)	0	5	
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2007	Summary of key changes: - Fax number was corrected - Updated the number of subjects planned for enrollment - Added clarification to the inclusion and exclusion criteria - Updated pharmacokinetic (PK) collection schedule - Updated vital sign and oxygen saturation measurement timing details - Updated blood, urine and sputum collection timings - Updated serious adverse event relatedness criteria
08 May 2007	Summary of key changes: - Updated the PK collection schedule - Updated the Schedule of In-Clinic Evaluations
27 September 2007	Summary of key changes: - Updated the exclusion criteria - Added clarification to the Post-Dose Pulmonary Function Testing schedule - Removed Post-Dose Sputum collection 4 hours post-dose - Added Data and Safety Monitoring Board (DSMB) meeting
16 June 2008	Summary of key changes: - Added information regarding the total number of treatment cycles - Added a Secondary Objective - Added treatment supplier details
05 August 2008	Summary of key changes: - The treatment follow-up period was extended - Study duration was increased
27 October 2008	Summary of key changes: - New text added regarding secondary endpoints - Added new text regarding the Extension Part - Main criteria for inclusion and exclusion was updated - Drug administration table added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported