Clinical trial results:
Long Term Safety and Tolerability Study of Open-Label Liposomal Amikacin for Inhalation (Arikace™) in Cystic Fibrosis Patients with Chronic Infection due to Pseudomonas aeruginosa

Summary

EudraCT number	2011-000443-24
Trial protocol	HU GB BE IE DE FR SE GR AT NL DK BG PL ES IT SK
Global end of trial date	16 July 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2020
First version publication date	26 June 2020

Trial information

Trial identification

Sponsor protocol code	TR02-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01316276
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
Scientific contact	Tom Vanthienen, Insmed Incorporated, +41 795432860, tom.vanthienen@insmed.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	04 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 July 2015
Global end of trial reached?	Yes
Global end of trial date	16 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the longer term safety, tolerability and efficacy of Arikace™ 560 mg administered once daily for up to twelve cycles with each cycle consisting of 28 days on-treatment followed by 28 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	01 August 2012
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	Netherlands: 2
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Serbia: 15
Worldwide total number of subjects	206
EEA total number of subjects	185

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)	32
Adolescents (12-17 years)	64
Adults (18-64 years)	110
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

206 subjects were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Liposomal Amikacin for Inhalation (LAI)

Arm description:

590 mg LAI once daily (QD) via a PARI Investigational eFlow® Nebulizer System (eFlow®) for 28 days followed by a 28-day off-treatment period. This cycle (28 days on treatment, 28 days off treatment) was to be repeated for up to 12 cycles, divided into 2 periods of 6 cycles each (approximately 12 months each).

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

Dosage and administration details:

• Liposomal amikacin for inhalation is provided as a sterile aqueous liposomal dispersion for inhalation via nebulization.
• 590 mg of liposomal amikacin for inhalation is administered once daily using the PARI Investigational eFlow® Nebulizer.
• Administration time is approximately 13 minutes.
• Liposomal amikacin for inhalation will be administered in two consecutive extension periods, each consisting of 6 cycles for a total of 12 cycles. Each cycle consists of 28 days on-treatment followed by 28 days off-treatment.

Number of subjects in period 1	Liposomal Amikacin for Inhalation (LAI)
Started	206
Completed	139
Not completed	67
Consent withdrawn by subject	24
Adverse event, non-fatal	19
Death	1
Other	22
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	206	206	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	32	32	
Adolescents (12-17 years)	64	64	
Adults (18-64 years)	110	110	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	21.0		
standard deviation	± 9.73	-	
Gender categorical Units: Subjects			
Female	103	103	
Male	103	103	
Race/Ethnicity Units: Subjects			
Caucasian (not of Hispanic origin)	200	200	
Hispanic	5	5	
African	1	1	
Geographic region Units: Subjects			
Western Europe / North America	99	99	
Central Europe / Eastern Europe	107	107	

End points

End points reporting groups

Reporting group title	Liposomal Amikacin for Inhalation (LAI)

Reporting group description:

590 mg LAI once daily (QD) via a PARI Investigational eFlow® Nebulizer System (eFlow®) for 28 days followed by a 28-day off-treatment period. This cycle (28 days on treatment, 28 days off treatment) was to be repeated for up to 12 cycles, divided into 2 periods of 6 cycles each (approximately 12 months each).

Primary: Treatment Emergent Adverse Events (TEAEs) up to Day 672

End point title	Treatment Emergent Adverse Events (TEAEs) up to Day 672[1]

End point description:

Treatment emergent adverse events including serious adverse events (SAE) and adverse events (AE) leading to permanent discontinuation of study drug

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Subjects with ≥1 treatment-emergent AE	183			
Subjects with ≥ 1 serious AE	92			
Subjects with ≥1 AE leading to discontinuation	21			

Statistical analyses

No statistical analyses for this end point

Primary: Laboratory Abnormalities up to Day 672

End point title	Laboratory Abnormalities up to Day 672[2]

End point description:

- Number of Subjects with Grade 3 or Higher Abnormalities in Clinical Laboratory Values
- Number of Subjects with Grade 3 or Higher Hematology Laboratory Value Abnormalities
- Number of Subjects with Grade 3 or Higher Chemistry Laboratory Value Abnormalities

End point type	Primary

End point timeframe:

Baseline, Day 377 and Day 672

Notes:

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

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Baseline	13			
Day 337/End of Study Year 1	8			
Day 672/End of Study Year 2	8			
Leukocytes (<2.0 × 109 /L)	7			
Lymphocytes (<0.5 × 109 /L)	12			
Neutrophils (<2.0 × 109 /L)	23			
Platelets (<192 × 109 /L)	1			
Alanine aminotransferase (>5.0 × ULN)	2			
Aspartate aminotransferase (>5.0 × ULN)	1			
Gamma-glutamyltransferase (>5.0 × ULN)	2			
Indirect bilirubin (>3.0 × ULN)	1			
Calcium (<2.1 mmol/L)	1			
Serum glucose: >13.9 mmol/L	14			
Serum glucose: < 2.2 mmol/L	6			
Phosphate (<0.6 mmol/L)	3			
Potassium: >6.0 mmol/L	8			
Potassium: <3.6 mmol/L	1			
Sodium: >155 mmol/L	1			
Sodium: <130 mmol/L	4			
Urate (> ULN with physiologic consequences)	8			

Statistical analyses

No statistical analyses for this end point

Primary: Acute Tolerability as Measured by Pulmonary Function Test (PFT) Changes Pre to Post Dose

End point title	Acute Tolerability as Measured by Pulmonary Function Test (PFT) Changes Pre to Post Dose[3]

End point description:

Number of Subjects with a >15% in Decline in Forced Expiratory Volume in 1 Second (FEV1) From Predose to Postdose.

End point type	Primary

End point timeframe:

Day 1, Day 84, Day 196, Day 281, Day 337, Day 449, Day 532 and Day 644

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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Day 1	6			
Day 84	6			
Day 196	1			
Day 281	5			
Day 337	5			
Day 449	6			
Day 532	2			
Day 644	3			

Statistical analyses

No statistical analyses for this end point

Primary: Respiratory Rate: Change From Baseline to Day 672

End point title	Respiratory Rate: Change From Baseline to Day 672[4]

End point description:

Respiratory rate was recorded at every visit as per standard practice at each investigational site.

Safety Population Subjects with missing data were excluded.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[4] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: breaths per minute				
arithmetic mean (standard deviation)	-0.8 (± 3.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Heart Rate: Change From Baseline From Day 672

End point title	Heart Rate: Change From Baseline From Day 672[5]

End point description:

Pulse rate (after at least 5-minute rest) was recorded at every visit as per standard practice at each investigational site.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[5] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: beats/min				
arithmetic mean (standard deviation)	-0.9 (± 12.46)			

Statistical analyses

No statistical analyses for this end point

Primary: Systolic BP: Change From Baseline at Day 672

End point title	Systolic BP: Change From Baseline at Day 672[6]

End point description:

Sitting blood pressure was recorded at every visit as per standard practice at each investigational site.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[6] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: mmHg				
arithmetic mean (standard deviation)	2.3 (± 11.39)			

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic BP: Change From Baseline at Day 672

End point title	Diastolic BP: Change From Baseline at Day 672[7]

End point description:

Sitting blood pressure was recorded at every visit as per standard practice at each investigational site.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[7] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: mmHg				
arithmetic mean (standard deviation)	1.5 (± 9.16)			

Statistical analyses

No statistical analyses for this end point

Primary: Body Temperature: Change From Baseline at Day 672

End point title	Body Temperature: Change From Baseline at Day 672[8]

End point description:

Body temperature was recorded at every visit as per standard practice at each investigational site.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[8] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Degrees Celcius				
arithmetic mean (standard deviation)	0.03 (± 0.316)			

Statistical analyses

No statistical analyses for this end point

Primary: Oxygen Saturation: Change From Baseline at Day 672

End point title	Oxygen Saturation: Change From Baseline at Day 672[9]

End point description:

Change in oxygen saturation as measured with pulse oximetry was performed via finger probes placed on the extremity opposite arterial lines and noninvasive blood pressure monitoring devices so that pulsatile flow was not interrupted.

End point type	Primary

End point timeframe:

From Study Initiation up to Day 672

Notes:

[9] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Percent of Hemoglobin				
arithmetic mean (standard deviation)	-0.1 (± 1.47)			

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Inhibitory Concentrations (MICs) for Pseudomonas Aeruginosa (Pa) and Burkholderia Species From Day 1 to Days 169, 337, 505 and 672

End point title	Minimum Inhibitory Concentrations (MICs) for Pseudomonas Aeruginosa (Pa) and Burkholderia Species From Day 1 to Days 169, 337, 505 and 672[10]

End point description:

Sputum was cultured for quantitative microbiological evaluation of Pa and Burkholderia species in designated regional central microbiology laboratories. A standard microbiology protocol was used for Pa culture and identification for each morphologically distinct Pa phenotype.

Although planned in the Statistical Analysis Plan (SAP), MICs of amikacin Burkholderia species were not determined due to the small number of isolates with Burkholderia. In addition, susceptibility testing of isolates of Pa and Burkholderia species against a panel of commonly used antipseudomonal antibiotics was planned but was not performed.

The results of the following analyses for Pa isolates are presented.
• Frequency of MIC of Amikacin
• Frequency of MIC of Tobramycin

MIC50: lowest concentration of the antibiotic at which 50 % of the isolates were inhibited.

Subjects with missing data were excluded.

End point type	Primary

End point timeframe:

Day 1, Day 169, Day 337, Day 505 and Day 672

Notes:

[10] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206[11]			
Units: µg/mL				
median (full range (min-max))				
Amikacin MIC50: Day 1	16.000 (2.00 to 2048.00)			
Amikacin MIC50: Day 169	16.000 (1.00 to 2048.00)			
Amikacin MIC50: Day 337	16.000 (2.00 to 2048.00)			
Amikacin MIC50: Day 505	16.000 (0.25 to 2048.00)			
Amikacin MIC50: Day 672	16.000 (1.00 to 2048.00)			
Tobramycin MIC50: Day 1	2.000 (0.25 to 1024.00)			
Tobramycin MIC50: Day 169	2.000 (0.12 to 1024.00)			
Tobramycin MIC50: Day 337	2.000 (0.25 to 1024.00)			
Tobramycin MIC50: Day 505	2.000 (0.12 to 1024.00)			
Tobramycin MIC50: Day 672	1.000 (0.12 to 1024.00)			

Notes:

[11] - Day 1: 180 subjects
Day 169: 159
Day 337: 143
Day 505: 119
Day 672: 109

Statistical analyses

No statistical analyses for this end point

Primary: Evaluation of Audiology

End point title	Evaluation of Audiology[12]

End point description:

Hearing was evaluated using air conduction [AC]. Bone conduction was required if the AC testing demonstrated a decrease of >20 decibels [dB]. Hearing loss was categorized using Common Terminology Criteria for Adverse Events as follows: GRADE 1 (best): Adults [A] on a Monitoring Program [MP]: Threshold shift of 15-25 dB; Pediatric [P]: Threshold shift >20 dB at 8 kilohertz (kHz). GRADE 2: [A] on a MP: Threshold shift of >25 dB; [A] not enrolled in MP: hearing loss; hearing aid/intervention not indicated; [P]: Threshold shift >20 dB at 4 kHz and above. GRADE 3: [A] enrolled in MP: Threshold shift of >25 dB; therapeutic intervention indicated; [A]: Not enrolled in MP: hearing aid/intervention; [P]: therapeutic intervention, including hearing aids: Threshold shift >20 dB at 3 kHz and above; additional speech-language related services. GRADE 4 (worst): [A]: Profound bilateral hearing loss; non-serviceable hearing; [P]: cochlear implant & additional speech-language related services.

End point type	Primary

End point timeframe:

Day 337 and Day 672

Notes:

[12] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Day 337 - None or minimal change	133			
Day 337 - Grade 1	2			
Day 337 - Grade 2	0			
Day 337 - Grade 3	0			
Day 337 - Grade 4	0			
Day 337 - Indeterminate	26			
Day 337 - Missing	45			
Day 672 - None or minimal change	120			
Day 672 - Grade 1	6			
Day 672 - Grade 2	0			
Day 672 - Grade 3	1			
Day 672 - Grade 4	0			
Day 672 - Indeterminate	7			
Day 672 - Missing	72			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Serum Creatinine Throughout the Study

End point title	Change in Serum Creatinine Throughout the Study[13]

End point description:

- Common Terminology Criteria for Adverse Events (CTCAE) Grade 1: > ULN-1.5 × ULN
- CTCAE Grade 2: > 1.5 × ULN to 3.0 x ULN

End point type	Primary

End point timeframe:

Baseline, Day 337 and Day 672

Notes:

[13] - 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: Summary statistics only were planned for this endpoint

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
CTCAE Grade 1: Baseline - Yes	1			
CTCAE Grade 1: Baseline - No	205			
CTCAE Grade 1: Day 337/End of Study Year 1 - Yes	0			
CTCAE Grade 1: Day 337/End of Study Year 1 - No	158			
CTCAE Grade 1: Day 672/End of Study Year 2 - Yes	0			
CTCAE Grade 1: Day 672/End of Study Year 2 - No	131			
CTCAE Grade 2: Baseline - Yes	0			
CTCAE Grade 2: Baseline - No	206			
CTCAE Grade 2: Day 337/End of Study Year 1 - Yes	0			
CTCAE Grade 2: Day 337/End of Study Year 1 - No	158			
CTCAE Grade 2: Day 672/End of Study Year 2 - Yes	0			
CTCAE Grade 2: Day 672/End of Study Year 2 - No	131			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in FEV1 Throughout the Study

End point title	Percent Change in FEV1 Throughout the Study

End point description:

Percent Change From Baseline in Predose FEV1.

Modified Intention to Treat (mITT) population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 and Day 672

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206[14]			
Units: Percent (%) change				
arithmetic mean (standard deviation)				
Baseline	2.104 (± 0.8650)			
Day 337	2.36 (± 14.359)			
Day 672	3.62 (± 18.485)			

Notes:

[14] - Day 337 = 158 subjects
Day 672 = 131 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing a Protocol Defined Pulmonary Exacerbation

End point title	Number of Subjects Experiencing a Protocol Defined Pulmonary Exacerbation

End point description:

For number of subjects to first protocol-defined pulmonary exacerbation, follow-up time began at the first dose of study drug (Day 1) and ended no later than Day 700 (28-day follow up).

End point type	Secondary

End point timeframe:

From Study Initiation up to Day 700

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Number of subjects with the event through Day 700	151			
Number censored	55			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Initiating Treatment

End point title	Number of Subjects Initiating Treatment

End point description:

The number of subjects initiating antipseudomonal therapy for protocol-defined pulmonary exacerbation confirmed by the investigator, and for investigator-defined pulmonary exacerbation were summarized.

The data presented below is the Frequency of Systemic or Inhaled Antipseudomonal Therapy for Protocol-defined Pulmonary Exacerbations Confirmed by Investigator.

Time to First Use of Any New Antibiotic Treatment, Censoring at Date of Last Contact.

End point type	Secondary

End point timeframe:

From Study Initiation up to Day 672

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
After Day 1 through Day 337	81			
After Day 1 through Day 672	108			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Received Antipseudomonal Antibiotic Treatment for Protocol Defined Pulmonary Exacerbation

End point title	Number of Subjects Who Received Antipseudomonal Antibiotic Treatment for Protocol Defined Pulmonary Exacerbation

End point description:

End point type	Secondary

End point timeframe:

From Study Initiation up to Day 700

End point values	Liposomal Amikacin for Inhalation (LAI)			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: Subjects				
Number of subjects with the event through Day 700	148			
Number censored	58			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment up to a maximum of 672 Days (end of study, year 2)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Liposomal Amikacin for Inhalation (LAI)

Reporting group description:

590 mg LAI QD via a PARI Investigational eFlow® Nebulizer System (eFlow®) for 28 days followed by a 28-day off-treatment period. This cycle (28 days on treatment, 28 days off treatment) was to be repeated for up to 12 cycles, divided into 2 periods of 6 cycles each (approximately 12 months each).

Serious adverse events	Liposomal Amikacin for Inhalation (LAI)		
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 206 (44.66%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal fluid rhinorrhoea			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			

subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological symptom				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Distal intestinal obstruction syndrome				
subjects affected / exposed	2 / 206 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal obstruction				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Rectal haemorrhage				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Haemoptysis				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	3 / 206 (1.46%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infective pulmonary exacerbation of cystic fibrosis				
subjects affected / exposed	81 / 206 (39.32%)			
occurrences causally related to treatment / all	27 / 139			
deaths causally related to treatment / all	0 / 1			
Appendicitis				

subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection pseudomonal				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Measles				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 206 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 206 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Liposomal Amikacin for Inhalation (LAI)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 206 (81.07%)		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 206 (9.22%)		
occurrences (all)	25		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 206 (6.31%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			

Haemoptysis			
subjects affected / exposed	30 / 206 (14.56%)		
occurrences (all)	69		
Cough			
subjects affected / exposed	27 / 206 (13.11%)		
occurrences (all)	45		
Dysphonia			
subjects affected / exposed	25 / 206 (12.14%)		
occurrences (all)	40		
Oropharyngeal pain			
subjects affected / exposed	16 / 206 (7.77%)		
occurrences (all)	26		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	129 / 206 (62.62%)		
occurrences (all)	359		
Nasopharyngitis			
subjects affected / exposed	52 / 206 (25.24%)		
occurrences (all)	88		
Upper respiratory tract infection			
subjects affected / exposed	32 / 206 (15.53%)		
occurrences (all)	64		
Pharyngitis			
subjects affected / exposed	18 / 206 (8.74%)		
occurrences (all)	20		
Rhinitis			
subjects affected / exposed	16 / 206 (7.77%)		
occurrences (all)	19		
Sinusitis			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	18		
Viral infection			
subjects affected / exposed	15 / 206 (7.28%)		
occurrences (all)	15		
Bronchitis			

subjects affected / exposed occurrences (all)	11 / 206 (5.34%) 15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2011	Summary of key changes: - Number of anticipated participants was updated - Exclusion criteria were updated - Schedule of assessments was updated - Details about the TR02-105 Extension were added - Summary of risks/benefits for ARIKACE™ treatment were added - Updates made to On-Treatment Study Site Procedures - Detail added to audiology testing section - Additional references added
14 November 2011	Summary of key changes: - Updated sponsor address - Updated introduction to include results from TR02-105 Extension study - Added clarification to exclusion criteria - Clarified that pregnancies need to be reported within the same timeframe as an SAE - Corrected visit window addition to Day 1 - Added clarification to prohibited medications section - Added clarifications to Study Evaluation section - Updated the date on the Investigator Drug Brochure in the references - Replaced the word "volume" with "liters" whenever FEV1 (volume) is used in the protocol
30 October 2013	Summary of key changes: - The delivered dose of 8mL per vial of 70mg/mL Arikace, which equates to a delivered dose of 560mg has been updated to 590mg throughout Amendment 3 - Removed reference to blinding for DMC and steering committee - Updated informed consent signing time frame - Added clarification text regarding early discontinuation visit - Added clarification text regarding study drug discontinuation criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported