Clinical trial results:
Randomized, open-label, active-controlled, multicenter study to assess the efficacy, safety and tolerability of Arikayce™ in Cystic Fibrosis patients with chronic infection due to Pseudomonas aeruginosa

Summary

EudraCT number	2011-000441-20
Trial protocol	HU GB BE IE DE AT GR NL DK ES IT BG SK
Global end of trial date	18 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 June 2020
First version publication date	13 June 2020

Trial information

Trial identification

Sponsor protocol code	TR02-108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01315678
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Insmed Incorporated
Sponsor organisation address	700 US Highway 202/206, Bridgewater, United States, NJ 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	14 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2013
Global end of trial reached?	Yes
Global end of trial date	18 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study are to evaluate the efficacy, safety and tolerability of 3 cycles (28 days on-treatment and 28 days off treatment) of Arikayce™ therapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Bulgaria: 36
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Serbia: 15
Worldwide total number of subjects	371
EEA total number of subjects	347

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)	51
Adolescents (12-17 years)	91
Adults (18-64 years)	229
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 70 sites in 18 countries.

Pre-assignment

Screening details:

A total of 371 subjects were screened, of which 302 subjects were randomized. 8 of the randomized subjects were not treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arikayce™

Arm description:

Arikayce™ is liposomal amikacin for inhalation.

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

Dosage and administration details:

Liposomal amikacin for inhalation (Arikayce™) using the PARI Investigational eFlow® Nebulizer: 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 for 3 cycles where each cycle consists of 28 days on-treatment followed by 28 days off-treatment.

Arm title	TOBI®

Arm description:

TOBI® is tobramycin inhalation solution.

Arm type	Active comparator
Investigational medicinal product name	Tobramycin
Investigational medicinal product code	
Other name	TOBI®
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Tobramycin inhalation solution using a PARI LC® Plus nebulizer. 300 mg tobramycin inhalation solution is administered twice a day using a PARI LC® Plus nebulizer.

- Nebulization time is approximately 20 minutes for each administration.
- Tobramycin inhalation solution will be administered for 3 cycles where each cycle consists of 28 days on-treatment followed by 28 days off-treatment

Number of subjects in period 1[1]	Arikayce™	TOBI®
Started	148	146
Completed	134	140
Not completed	14	6
Consent withdrawn by subject	7	3
Adverse event, non-fatal	3	1
Similar reason to those listed below	3	2
Lost to follow-up	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: Worldwide enrollment number includes 69 subjects that were screened but not randomized and 8 subjects that were randomized but not treated. Baseline period includes analysis for the modified intent-to-treat population (mITT; received at least 1 dose of study drug).

Baseline characteristics

Reporting groups	
Reporting group title	Arikayce™
Reporting group description:	
Arikayce™ is liposomal amikacin for inhalation.	
Reporting group title	TOBI®
Reporting group description:	
TOBI® is tobramycin inhalation solution.	

Reporting group values	Arikayce™	TOBI®	Total
Number of subjects	148	146	294
Age categorical Units: Subjects			
6 - 12 years	27	26	53
>12 - 18 years	34	33	67
>18 years	87	87	174
Gender categorical Units: Subjects			
Female	69	70	139
Male	79	76	155
Ethnicity Units: Subjects			
Caucasian	139	141	280
Hispanic	5	3	8
African	1	0	1
Other	3	1	4
Not recorded	0	1	1

End points

End points reporting groups

Reporting group title	Arikayce™
Reporting group description:	
Arikayce™ is liposomal amikacin for inhalation.	
Reporting group title	TOBI®
Reporting group description:	
TOBI® is tobramycin inhalation solution.	

Primary: Pulmonary Function Test: Forced Expiratory Volume in 1 Second (FEV1)

End point title	Pulmonary Function Test: Forced Expiratory Volume in 1 Second (FEV1)[1]
End point description:	
Relative Change (%) from baseline to end of study (Day 168) in FEV1 (1 second).	
End point type	Primary
End point timeframe:	
Baseline to Day 168	

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: No additional statistical analysis was planned for this endpoint.

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	137		
Units: percentage (%) change				
arithmetic mean (standard deviation)	0.47 (± 13.930)	1.67 (± 16.050)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pumonary Function Test: Forced Expiratory Volume in 1 Second (FEV1)

End point title	Pumonary Function Test: Forced Expiratory Volume in 1 Second (FEV1)
End point description:	
Relative changes (%) from baseline to Study Days 14, 28, 57, 84, 113, 140, 168 in FEV1.	
End point type	Secondary
End point timeframe:	
Baseline, Day 14, Day 28, Day 57, Day 84, Day 113, Day 140 and Day 168	

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: percentage (%) change				
arithmetic mean (standard deviation)				
Day 14	2.59 (± 13.332)	6.64 (± 15.669)		
Day 28	0.79 (± 14.745)	3.32 (± 14.715)		
Day 57	-3.49 (± 12.319)	0.70 (± 14.510)		
Day 84	0.44 (± 14.350)	3.59 (± 14.642)		
Day 113	-0.90 (± 12.028)	0.42 (± 14.434)		
Day 140	0.43 (± 15.299)	1.37 (± 16.563)		
Day 168	-0.12 (± 14.326)	1.58 (± 15.970)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing a Pulmonary Exacerbation

End point title	Number of Subjects Experiencing a Pulmonary Exacerbation

End point description:

Number of subjects experiencing a pulmonary exacerbation measured by number with event and number censored.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: Subjects				
Number with Event	73	63		
Number Censored	75	83		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Comparison groups	Arikayce™ v TOBI®

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.13

Secondary: Number of Subjects who received Antipseudomonal Antibiotic Treatment for Pulmonary Exacerbation

End point title	Number of Subjects who received Antipseudomonal Antibiotic Treatment for Pulmonary Exacerbation

End point description:

Number of subjects who experienced antipseudomonal antibiotic treatment for pulmonary exacerbation measured by number with event and number censored.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: Subjects				
Number with Event	55	48		
Number Censored	93	98		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Comparison groups	Arikayce™ v TOBI®
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6031
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.66

Secondary: Number of Subjects who experienced All-Cause Hospitalization

End point title	Number of Subjects who experienced All-Cause Hospitalization
End point description:	
Number of subjects with first all cause hospitalization measured by number with event and number censored.	
End point type	Secondary
End point timeframe:	
Baseline to Day 168	

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: Subjects				
Number with Event	24	29		
Number Censored	124	117		

Statistical analyses

Statistical analysis title	Stratified Cox proportional hazards model
Comparison groups	Arikayce™ v TOBI®
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4861
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.44

Secondary: Change in Density (Log CFU) in Pseudomonas Aeruginosa in Sputum

End point title	Change in Density (Log CFU) in Pseudomonas Aeruginosa in

	Sputum

End point description:

Change in density (Log CFU) from baseline in Pseudomonas aeruginosa in sputum.

End point type	Secondary

End point timeframe:

Baseline, Day 14, Day 28, Day 57, Day 84, Day 113, Day 140 and Day 168

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: Log 10 CFU				
arithmetic mean (standard deviation)				
Baseline	6.872 (± 1.8806)	6.510 (± 2.3202)		
Day 14	-1.124 (± 2.0542)	-1.663 (± 2.4017)		
Day 28	-1.208 (± 2.1594)	-1.453 (± 2.4440)		
Day 57	-0.210 (± 1.9874)	-0.098 (± 1.7446)		
Day 84	-0.945 (± 2.2223)	-1.182 (± 2.6914)		
Day 113	-0.613 (± 2.1928)	-0.135 (± 2.3461)		
Day 140	-1.440 (± 2.4357)	-1.315 (± 2.2300)		
Day 168	-0.725 (± 2.0073)	-0.136 (± 2.1750)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Percentage (%) Change in Respiratory Symptoms as Measured by the CFQ-R

End point title	Relative Percentage (%) Change in Respiratory Symptoms as Measured by the CFQ-R

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 patients 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.

End point type	Secondary

End point timeframe:

Baseline, Day 14, Day 28, Day 57, Day 84, Day 113, Day 140 and Day 168

End point values	Arikayce™	TOBI®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	146		
Units: percentage (%) change				
arithmetic mean (standard error)				
Day 14	13.65 (± 2.995)	8.81 (± 3.019)		
Day 28	15.54 (± 3.363)	11.03 (± 3.419)		
Day 57	8.00 (± 3.120)	7.97 (± 3.146)		
Day 84	13.20 (± 3.079)	8.55 (± 3.111)		
Day 113	3.58 (± 3.323)	5.03 (± 3.290)		
Day 140	13.84 (± 3.060)	6.10 (± 3.079)		
Day 168	12.06 (± 3.784)	8.07 (± 3.790)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to Day 168	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0
Reporting groups	
Reporting group title	Arikayce™
Reporting group description:	
Arikayce™ is liposomal amikacin for inhalation.	
Reporting group title	TOBI®
Reporting group description:	
TOBI® is tobramycin inhalation solution.	

Serious adverse events	Arikayce™	TOBI®	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 148 (17.57%)	29 / 146 (19.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 148 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 148 (0.68%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 148 (0.68%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 146 (0.68%)	
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			
Bronchial secretion retention			
subjects affected / exposed	1 / 148 (0.68%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 148 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	24 / 148 (16.22%)	23 / 146 (15.75%)	
occurrences causally related to treatment / all	8 / 28	4 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 148 (0.00%)	2 / 146 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 146 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 146 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arikayce™	TOBI®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 148 (77.03%)	91 / 146 (62.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 148 (8.11%)	5 / 146 (3.42%)	
occurrences (all)	22	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 148 (6.76%)	5 / 146 (3.42%)	
occurrences (all)	12	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 148 (12.16%)	11 / 146 (7.53%)	
occurrences (all)	23	24	
Dysphonia			
subjects affected / exposed	18 / 148 (12.16%)	8 / 146 (5.48%)	
occurrences (all)	28	9	
Haemoptysis			

subjects affected / exposed	24 / 148 (16.22%)	10 / 146 (6.85%)	
occurrences (all)	53	19	
Oropharyngeal pain			
subjects affected / exposed	11 / 148 (7.43%)	6 / 146 (4.11%)	
occurrences (all)	12	7	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	74 / 148 (50.00%)	59 / 146 (40.41%)	
occurrences (all)	111	91	
Nasopharyngitis			
subjects affected / exposed	24 / 148 (16.22%)	33 / 146 (22.60%)	
occurrences (all)	29	43	
Rhinitis			
subjects affected / exposed	9 / 148 (6.08%)	9 / 146 (6.16%)	
occurrences (all)	10	9	
Upper respiratory tract infection			
subjects affected / exposed	15 / 148 (10.14%)	9 / 146 (6.16%)	
occurrences (all)	21	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2011	Updates were made to the following sections of the protocol: - Clinical experience - Potential risks - Summary of risks/benefits - Study drug - Study evaluations - Assessment of safety - References sections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported