Clinical trial results:
Safety and Tolerability Study of SLIT™ Amikacin 500mg Once Daily for 14 Days by Inhalation in Cystic Fibrosis Study Subjects Chronically Infected with Pseudomonas Aeruginosa

Summary

EudraCT number	2005-004389-17
Trial protocol	HU
Global end of trial date	18 September 2006

Results information

Result version number	v2 (current)
This version publication date	01 June 2023
First version publication date	29 July 2020
Version creation reason	
Summary attachment (see zip file)	CSR synopsis (20200331 TR02-103 synopsis redacted final.pdf)

Trial information

Trial identification

Sponsor protocol code	TR02-103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	Insmed Medical Information, Insmed Incorporated, medicalinformation@Insmed.com
Scientific contact	Insmed Medical Information, Insmed Incorporated, medicalinformation@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?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 September 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of nebulized amikacin in a sustained release lipid inhalation targeting (SLIT)™ formulation administered 500 milligrams (mg) once daily (QD) for 14 days.

Protection of trial subjects:

This trial 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 of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 2006
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	Hungary: 11
Country: Number of subjects enrolled	Serbia: 2
Worldwide total number of subjects	13
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in this trial at investigative sites in Serbia and Hungary from 14 April 2006 to 18 September 2006.

Pre-assignment

Screening details:

13 subjects with cystic fibrosis (CF), chronically infected with Pseudomonas aeruginosa were enrolled and received Amikacin in a SLIT™ formulation (Arikace™) by inhalation.

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	Amikacin 500 mg

Arm description:

Subjects received amikacin 500 mg QD by inhalation for 14 days.

Arm type	Experimental
Investigational medicinal product name	SLIT™ Amikacin
Investigational medicinal product code	
Other name	Arikace™
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Nasal use

Dosage and administration details:

Inhalation dispersion administered via nasal route by means of a nebuliser and compressor.

Number of subjects in period 1	Amikacin 500 mg
Started	13
Completed	13

Baseline characteristics

Reporting groups	
Reporting group title	Amikacin 500 mg
Reporting group description:	
Subjects received amikacin 500 mg QD by inhalation for 14 days.	

Reporting group values	Amikacin 500 mg	Total	
Number of subjects	13	13	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	8	8	
Gender Categorical Units: Subjects			
Female	7	7	
Male	6	6	
Race Units: Subjects			
Caucasian	13	13	
Ethnicity Units: Subjects			
Not Hispanic or Latino	13	13	
Forced Expiratory Volume in 1 Second (FEV1)			
FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation.			
Units: Litres			
arithmetic mean	2.30		
standard deviation	± 0.82	-	
Forced Vital Capacity (FVC)			
FVC is measured during a spirometry test, also known as a pulmonary function test, which involves forcefully breathing out into a mouthpiece connected to a spirometer machine. FVC is the volume of air that can be forcibly and completely blown out after full inspiration.			
Units: Litres			
arithmetic mean	3.28		
standard deviation	± 0.88	-	
FEV1 Percent (%) Predicted			
FEV1 (measured by handheld spirometer) is the volume of air that can be forcibly exhaled from the lungs in the first second. The percent predicted FEV1 equals the subject's observed FEV1 divided by the subject's predicted FEV1 (determined by height and race) and converted to a percentage by multiplying by 100%.			
Units: percent			
arithmetic mean	63.80		
standard deviation	± 16.71	-	
Forced Expiratory Flow (FEF) 25-75%			
The FEF 25%-75% (measured by handheld spirometer) is the forced expiratory flow from 25% to 75% of FVC (volume of air that can be forcibly and completely blown out after full inspiration).			
Units: Litres per second (L/sec)			
arithmetic mean	1.62		
standard deviation	± 1.04	-	

Vital Capacity (VC)			
The vital capacity is called the sum total volume of air that can be expired after maximum inhalation or maximum air that a subject can breathe in after forced expiration and is an important indicator of a subject’s respiratory health.			
Units: Litres			
arithmetic mean	3.23		
standard deviation	± 0.82	-	

End points

End points reporting groups

Reporting group title	Amikacin 500 mg
Reporting group description:	
Subjects received amikacin 500 mg QD by inhalation for 14 days.	

Primary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs)[1]
End point description:	
An adverse event is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. Intent-to-Treat (ITT) Population included all subjects who received any amount of study drug.	
End point type	Primary
End point timeframe:	
From first dose of study drug up to last follow-up visit (Day 42)	

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes in Vital Signs[2]
End point description:	
Vital sign measurements included heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation. ITT Population included all subjects who received any amount of study drug.	
End point type	Primary
End point timeframe:	
From first dose of study drug up to last follow-up visit (Day 42)	

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Quality of Life Questionnaire Total Score

End point title	Change From Baseline in Quality of Life Questionnaire Total Score[3]

End point description:

The cystic fibrosis quality of life questionnaire revised (CFQ-R), a validated disease-specific instrument that measures health-related quality of life (HRQOL) for adolescents and adults with CF. It is self-administered and consists of 44 items, divided into 12 generic and disease-specific scales. The scale includes physical functioning, role, vitality, emotional functioning, social functioning, body image, eating disturbances, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms. Scale range: 0 to 100 (maximum). Higher values indicate better quality of life. ITT Population included all subjects who received any amount of study drug. 9999 indicates that the data is not available as descriptive analysis to generate summarised data was not performed.

End point type	Primary

End point timeframe:

Days 1 and 15

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 analyses were planned for this endpoint.

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: score on a scale				
least squares mean (standard error)				
Day 1	9999 (± 9999)			
Day 15	9999 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in FEV1 at Day 42

End point title	Change From Baseline in FEV1 at Day 42[4]

End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline, Day 42

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litres				
arithmetic mean (standard deviation)	0.31 (± 0.42)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Oxygen Saturation (SaO2)

End point title	Percentage of Oxygen Saturation (SaO2)[5]

End point description:

ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

At last follow-up visit (Day 42)

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage on room air				
arithmetic mean (standard deviation)	97.69 (± 0.75)			

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Function Test : Change From Baseline in FVC at Day 42

End point title	Pulmonary Function Test : Change From Baseline in FVC at Day 42[6]

End point description:

FVC is measured during a spirometry test, also known as a pulmonary function test, which involves forcefully breathing out into a mouthpiece connected to a spirometer machine. FVC is the volume of air that can be forcibly and completely blown out after full inspiration. ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline, Day 42

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litres				
arithmetic mean (standard deviation)	0.23 (± 0.38)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities[7]

End point description:

Laboratory assessments included analysis of hematology (hemoglobin, hematocrit, white blood cells [WBC], neutrophils, platelets) and serum chemistry (blood urea nitrogen [BUN], creatinine, sodium, carbon dioxide, phosphate, gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, total cholesterol, low-density lipoprotein [LDL] and high-density lipoprotein [HDL], glucose, total protein, albumin, uric acid). Any abnormal value observed was to be flagged to the attention of the investigator who was to judge whether the finding was clinically significant. ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to last follow-up visit (Day 42)

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
Hematology	2			
Serum Chemistry	5			

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Function Test: Change From Baseline in Percentage of Predicted FEV1 at Day 42

End point title	Pulmonary Function Test: Change From Baseline in Percentage of Predicted FEV1 at Day 42[8]

End point description:

FEV1 (measured by handheld spirometer) is the volume of air that can be forcibly exhaled from the lungs in the first second. The percent predicted FEV1 equals the subject's observed FEV1 divided by the subject's predicted FEV1 (determined by height and race) and converted to a percentage by multiplying by 100%. ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline, Day 42

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage				
arithmetic mean (standard deviation)	8.31 (± 9.40)			

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Function Test: Change From Baseline in FEF During mid Expiration 25-75% at Day 42

End point title	Pulmonary Function Test: Change From Baseline in FEF During mid Expiration 25-75% at Day 42[9]

End point description:

The FEF 25%-75% (measured by handheld spirometer) is the forced expiratory flow from 25% to 75% of FVC (volume of air that can be forcibly and completely blown out after full inspiration). ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline, Day 42

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: L/sec				
arithmetic mean (standard deviation)	0.69 (± 1.08)			

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Function Test: Change From Baseline in VC at Day 42

End point title	Pulmonary Function Test: Change From Baseline in VC at Day 42[10]

End point description:

The vital capacity is called the sum total volume of air that can be expired after maximum inhalation or maximum air that a subject can breathe in after forced expiration and is an important indicator of a subject's respiratory health. ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline, Day 42

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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litres				
arithmetic mean (standard deviation)	0.14 (± 0.30)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Positive Sputum Culture for Pseudomonas Aeruginosa

End point title	Number of Subjects With Positive Sputum Culture for Pseudomonas Aeruginosa[11]

End point description:

ITT Population included all subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

Day 42

Notes:

[11] - 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: Only descriptive analysis was planned to be reported for this endpoint

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Density of Pseudomonas Aeruginosa in Sputum at Day 14

End point title	Change From Baseline in Density of Pseudomonas Aeruginosa in Sputum at Day 14

End point description:

Density of Pseudomonas aeruginosa in sputum was measured in colony forming units per gram (CFU/g). ITT Population included all subjects who received any amount of study drug.

End point type	Secondary

End point timeframe:

Baseline, Day 14

End point values	Amikacin 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: CFU/g				
arithmetic mean (confidence interval 95%)	-1.09 (-2.09 to -0.09)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to last follow-up visit (Day 42)	
Adverse event reporting additional description:	
ITT Population included all subjects who received any amount of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Amikacin 500 mg
Reporting group description:	
Subjects received amikacin 500 mg QD by inhalation for 14 days.	

Serious adverse events	Amikacin 500 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Amikacin 500 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood albumin decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Blood glucose increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Respiratory, thoracic and mediastinal disorders Haemoptysis subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Renal and urinary disorders Renal cyst subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2		
Infections and infestations			

Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus (incl subtypes) subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2005	The following changes were implemented with Amendment 1: -The word "randomisation" was revised to read "registration". -Specialist oral pharyngeal assessment was added to the pre-treatment complete physical exam. -Chest x-ray at Visit 42 was added to the off study evaluations. -Blood and sputum PK assessment at Visit 1 screening indicated was deleted. -Specialist oral pharyngeal assessment prior to Day 1 and Day 21 and other visits if clinically indicated was added. -Chest x-ray at follow-up was changed to Day 42 and if clinically indicated. -Devilbiss compressor was changed to EasyComp compressor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported