Clinical trial results:
A Randomized, Open Label, Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Patients with Nontuberculous Mycobacterial (NTM) Lung Infections Caused by Mycobacterium avium complex (MAC) That are Refractory to Treatment

Summary

EudraCT number	2014-005010-31
Trial protocol	DE AT IT NL ES PL SE
Global end of trial date	03 April 2019

Results information

Result version number	v1 (current)
This version publication date	17 April 2020
First version publication date	17 April 2020

Trial information

Trial identification

Sponsor protocol code	INS-212

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02344004
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 Inc, +41 795432860, tom.vanthienen@insmed.com
Scientific contact	Tom Vanthienen, Insmed Inc, +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	09 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, for achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 compared to a multi-drug regimen alone

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:

Throughout the duration of the study, subjects in both arms of the study continued the same multidrug (at least 2antibiotics) antimycobacterial regimen. The regimen was based on the 200 7ATS/IDSA (American Thoracic Society/Infectious Diseases Society of America) guidelines or respective local guidelines, and they were not to change during the treatment phase except for safety concerns or if rescue antimycobacterial therapy was required.

Evidence for comparator: -

Actual start date of recruitment	28 February 2015
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	Australia: 40
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 22
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	United States: 219
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 12

Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	492
EEA total number of subjects	114

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	223
From 65 to 84 years	263
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 127 sites in 18 countries.

Pre-assignment

Screening details:

Disposition table reflects the disposition through end of the study (Month 28).

The deaths under Reasons for Discontinuation reflect the primary reason (according to investigator's judgment) that the subject discontinued and does not represent all deaths in the trial.

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	LAI + Multi-drug Regimen

Arm description:

Subjects received Liposomal Amikacin for Inhalation (LAI) 590 mg once daily (QD) in addition to their already prescribed anti-mycobacterial regimen (based on the 2007 American Thoracic Society/Infectious Diseases Society of America [ATS/IDSA] Guidelines); LAI 590 mg QD, administered by inhaling drug product that had been aerosolized in an eFlow nebulizer over approximately 14 minutes

Arm type	Experimental
Investigational medicinal product name	LAI
Investigational medicinal product code	
Other name	Liposomal Amikacin for Inhalation
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

590 mg once daily (QD)

Investigational medicinal product name	MDR
Investigational medicinal product code	
Other name	Multi Drug Regimen
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

variable depending on the medication

Arm title	Multi-drug Regimen

Arm description:

Subjects received their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines)

Arm type	Standard of Care
Investigational medicinal product name	MDR
Investigational medicinal product code	
Other name	Multi Drug Regimen
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:
variable depending on the medication

Number of subjects in period 1[1]	LAI + Multi-drug Regimen	Multi-drug Regimen
Started	224	112
Completed	163	98
Not completed	61	14
Adverse event, serious fatal	9	7
Consent withdrawn by subject	22	5
Physician decision	4	1
Adverse event, non-fatal	11	1
Rescue Medication	2	-
Protocol deviation	1	-
Other not specified	12	-

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: The number 492 represents how many subjects were screened. Of these, 336 were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	LAI + Multi-drug Regimen
Reporting group description:	
Subjects received Liposomal Amikacin for Inhalation (LAI) 590 mg once daily (QD) in addition to their already prescribed anti-mycobacterial regimen (based on the 2007 American Thoracic Society/Infectious Diseases Society of America [ATS/IDSA] Guidelines); LAI 590 mg QD, administered by inhaling drug product that had been aerosolized in an eFlow nebulizer over approximately 14 minutes	
Reporting group title	Multi-drug Regimen
Reporting group description:	
Subjects received their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines)	

Reporting group values	LAI + Multi-drug Regimen	Multi-drug Regimen	Total
Number of subjects	224	112	336
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	64.6	64.9	
standard deviation	± 9.59	± 10.16	-
Gender categorical Units: Subjects			
Female	165	68	233
Male	59	44	103
Ethnicity Units: Subjects			
Hispanic or Latino	10	5	15
Not Hispanic or Latino	211	102	313
Unknown or Not Reported	3	5	8
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	58	25	83
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	3	3	6
White	158	77	235
More than one race	1	0	1

Unknown or Not Reported	3	6	9
If female, is subject of childbearing potential? Units: Subjects			
Yes	13	6	19
No	152	62	214
Not female	59	44	103
If not childbearing potential, specify Units: Subjects			
Postmenopausal	114	50	164
Surgically sterile	38	12	50
Naturally sterile	0	0	0
Female of childbearing potential	13	6	19
Not female	59	44	103
Region Units: Subjects			
North America	104	55	159
Asia (excluding Japan)	14	6	20
Japan	34	14	48
Rest of World	72	37	109
Multidrug regimen prior to enrollment Units: Subjects			
On treatment	201	101	302
Off treatment for at least 3 months	23	11	34
Smoking status (includes ecigarettes) Units: Subjects			
Current smoker	26	10	36
Not a current smoker	198	102	300
Prior nebulized IV amikacin Units: Subjects			
Prior nebulized IV amikacin	24	15	39
No prior nebulized IV amikacin	200	97	297

End points

End points reporting groups

Reporting group title	LAI + Multi-drug Regimen

Reporting group description:

Subjects received Liposomal Amikacin for Inhalation (LAI) 590 mg once daily (QD) in addition to their already prescribed anti-mycobacterial regimen (based on the 2007 American Thoracic Society/Infectious Diseases Society of America [ATS/IDSA] Guidelines); LAI 590 mg QD, administered by inhaling drug product that had been aerosolized in an eFlow nebulizer over approximately 14 minutes

Reporting group title	Multi-drug Regimen

Reporting group description:

Subjects received their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines)

Primary: Number of Subjects Achieving Culture Conversion by Month 6 in the Liposomal Amikacin for Inhalation (LAI) + Multidrug Regimen (MDR) Arm Compared to the MDR Alone Arm

End point title	Number of Subjects Achieving Culture Conversion by Month 6 in the Liposomal Amikacin for Inhalation (LAI) + Multidrug Regimen (MDR) Arm Compared to the MDR Alone Arm

End point description:

Sputum specimens were collected at Screening (Visit 1), Baseline (Visit 2), and at Visits 3 (Month 1) through 8 (Month 6). A negative culture result reflected a negative culture result for all sputum samples collected at each visit. Subjects met the primary endpoint of culture conversion by Month 6 if they had 3 consecutive monthly MAC-negative sputum cultures during the first 6 months of the study. A subject needed to achieve the first of 3 consecutive negative sputum cultures (that defined culture conversion) by Month 4 in order to meet the primary endpoint by Month 6. Each subject in the intent to treat (ITT) population (ie, all randomized subjects) was classified as either a converter or non-converter by Month 6.

End point type	Primary

End point timeframe:

by Month 6

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: subjects				
Converter	65	10		
Non-converter	159	102		

Statistical analyses

Statistical analysis title	Summary of Month 6 Conversion Rates

Statistical analysis description:

The proportion of subjects achieving culture conversion by Month 6 was analyzed using the Cochran-Mantel-Haenszel test, stratified by smoking status and prior multi-drug regimen. The treatment comparison was tested at two-sided significance level of 0.05. The null hypothesis assumed that culture

conversion by Month 6 is independent of treatment, and the alternative hypothesis assumed that culture conversion by Month 6 is associated with treatment.

Comparison groups	LAI + Multi-drug Regimen v Multi-drug Regimen
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The final analysis of the primary endpoint, the number of subjects achieving culture conversion at by Month 6, was performed after the last subjects completed Month 6 and his/her Month 6 sputum culture result was available.

Primary: Number of Subjects Achieving Durable Culture Conversion Through 3 Months Off Treatment in the LAI + MDR Arm Compared to the MDR Arm Alone

End point title	Number of Subjects Achieving Durable Culture Conversion Through 3 Months Off Treatment in the LAI + MDR Arm Compared to the MDR Arm Alone

End point description:

Sputum specimens were collected at screening, baseline (Day 1), during treatment, and at Months 1, 3, 6, and 12 months off treatment. Culture conversion with durability was defined as achieving culture conversion by Month 6 and then having no more than 2 consecutive broth positive cultures and no Agar positive culture up to 3 months off treatment. Converters with missing broth or Agar sputum culture result after Month 6 up to 3 months off treatment were considered as not achieving culture conversion with durability except those subjects who are unable to produce sputum despite reasonable efforts, as reported by source documentation. Subjects who had relapse/recurrence, had "rescue" medication and/or died before reaching 3 months off treatment were considered as not achieving culture conversion with durability.

End point type	Primary

End point timeframe:

Up to Month 19

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: subjects				
Durable Conversion	36	0		
Non-durable Conversion	188	112		

Statistical analyses

Statistical analysis title	Summary of Durable Culture Conversion
Comparison groups	LAI + Multi-drug Regimen v Multi-drug Regimen
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline (Day 1) to Month 6 in the Six-Minute Walk Test (6MWT) Distance in the LAI + MDR Arm Compared to the MDR Alone Arm

End point title	Change From Baseline (Day 1) to Month 6 in the Six-Minute Walk Test (6MWT) Distance in the LAI + MDR Arm Compared to the MDR Alone Arm

End point description:

A 6-minute walk assessment of exertional capability was performed at Baseline (Day 1) and at Month 6. The standardized protocol based on the ATS guidelines was used. The 6MWT was conducted by a site member who was blinded to the subject's open-label treatment assignment. The analysis of the change from Baseline (Day 1) to Month 6 in the 6MWT distance was performed after the last subject completed Month 6 and his/her 6MWT distance data were available.

End point type	Secondary

End point timeframe:

at Month 6

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	112		
Units: meters				
arithmetic mean (standard deviation)				
Baseline	424.2 (± 1.12)	420.9 (± 0.48)		
Month 6	420.6 (± 4.73)	420.3 (± 2.57)		
Change from Baseline to Month 6	-3.6 (± 3.25)	-0.5 (± 4.20)		

Statistical analyses

Statistical analysis title	Summary of 6MWT

Statistical analysis description:

This was analyzed using a mixed model repeated measures (MMRM) analysis of change from Baseline at Months 4&6. MMRM included treatment, month, treatment-by-month interaction, combination of smoking status & prior MDR (4 levels: Yes/Yes, Yes/No, No/Yes, and No/No) as fixed factors, baseline 6MWD as a covariate & baseline 6MWD-by-month interaction. An unstructured covariance matrix was used for the MMRM.

Baseline is defined as the last non-missing value prior to first dose of study drug.

Comparison groups	Multi-drug Regimen v LAI + Multi-drug Regimen
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.7804 [3]
Method	Mixed Model Repeated Measures (MMRM)

Notes:

[2] - Statistics were obtained from an mixed-effects model repeated measures (MMRM) model with pattern-mixture modeling of missing values due to dropout, which included treatment, month, the treatment-by-month interaction, and the combination of smoking status and prior multidrug regimen as fixed factors, the baseline 6MWT distance as a covariate and baseline 6MWT distance-by-month interaction. MMRM included post postbaseline data through Month 6.

[3] - For baseline, n is the number of subjects with a baseline score and at least 1 postbaseline score. For Month 6, n is the number of subjects with a baseline score and a postbaseline score at the summarized visit.

Secondary: Time to Culture Conversion by Month 6 in the LAI + MDR Arm Compared to the MDR Alone Arm

End point title	Time to Culture Conversion by Month 6 in the LAI + MDR Arm Compared to the MDR Alone Arm

End point description:

The time to culture conversion was defined by the date of the first of at least 3 consecutive monthly culture specimens that were Mycobacterium avium complex (MAC)-negative.

The 25th percentile time to conversion is the estimated time taken for 25% of subjects to convert.

The 50th percentile time to conversion is the estimated time taken for 50% of subjects to convert.

The 25th percentile time to conversion could not be estimated for the Multi-drug Regimen arm due to an insufficient proportion of subjects achieving culture conversion by Month 6.

The 50th percentile time to conversion could not be estimated for either arm due to an insufficient proportion of patients achieving culture conversion by Month 6.

End point type	Secondary

End point timeframe:

By Month 6

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: months				
number (confidence interval 95%)				
25th Percentile	2.13 (1.83 to 3.87)	99999 (99999 to 99999)		
50th Percentile	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Summary of Time to Culture Conversion

Statistical analysis description:

Kaplan Meier estimates for the distribution of time to culture conversion were constructed for treatment arms. The treatment comparison was made using the stratified log rank test for the ITT population. The estimated median time to culture conversion for each treatment arm was not estimable. The time to culture conversion was analyzed using Cox regression model to estimate hazards ratio.

Comparison groups	Multi-drug Regimen v LAI + Multi-drug Regimen
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	3.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.01
upper limit	7.63

Secondary: Number of Subjects Achieving Sustained Culture Conversion at the End of Treatment (EOT) in the LAI + MDR Arm Compared to the MDR Arm Alone

End point title	Number of Subjects Achieving Sustained Culture Conversion at the End of Treatment (EOT) in the LAI + MDR Arm Compared to the MDR Arm Alone

End point description:

Sustained conversion was evaluated in subjects who completed at least 12 months of treatment from the start of culture conversion. Sustained conversion was defined as conversion (3 consecutive negative monthly sputum samples) by Month 6 with no positive agar media culture or no more than 2 broth media cultures up to and including the time point. Subjects who did not convert were considered non-sustained conversions.

End point type	Secondary

End point timeframe:

up to Month 16

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: subjects				
Sustained Conversion	41	3		
Non-Sustained Conversion	183	109		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 6-Minute Walk Test (6MWT) Distance at EOT in the LAI Arm Compared to a Multi-drug Regimen Alone

End point title	Change in 6-Minute Walk Test (6MWT) Distance at EOT in the LAI Arm Compared to a Multi-drug Regimen Alone

End point description:

A 6-minute walk assessment of exertional capability was performed at Baseline (Day 1) and up to EOT or Month 16. The standardized protocol based on the ATS guidelines was used. The 6MWT was conducted by a site member who was blinded to the subject's open-label treatment assignment.

Due to the widely varying timepoints that makeup the EOT visit, this was not considered an appropriate analysis and was not performed.

End point type	Secondary

End point timeframe:

up to Month 16

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: subjects				

Notes:

[4] - Refer to endpoint description

[5] - Refer to endpoint description

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (Day 1) at Month 6 in the St. George's Respiratory Questionnaire (SGRQ) Total Score

End point title	Change From Baseline (Day 1) at Month 6 in the St. George's Respiratory Questionnaire (SGRQ) Total Score

End point description:

The SGRQ was completed before administration of study drug at Baseline (Day 1) and Months 3, 6, 8, and 12, and at the EOT visit and the 3 months off treatment visit. The SGRQ is a self-administered questionnaire that has been validated in subjects with airways disease, specifically in subjects with bronchiectasis. The SGRQ assesses health-related quality of life in subjects with chronic pulmonary disease by evaluating 3 health domains: symptoms (distress caused by respiratory symptoms); activity (effects of disturbances on mobility and physical activity); and impacts (the effect of disease on factors such as employment, personal control of one's health, and need for medication). A composite total score is derived as the sum of domain scores for symptoms, activity, and impact (0=the best possible score and 100=the worst possible score). A within patient reduction from baseline in score of 4 units is generally recognized as a clinically meaningful improvement in quality of life.

End point type	Secondary

End point timeframe:

At Month 6

End point values	LAI + Multi-drug Regimen	Multi-drug Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[6]	112[7]		
Units: score on a scale				
arithmetic mean (standard deviation)				
SGRQ Total Score at Baseline	36.555 (± 21.3777)	38.409 (± 21.5753)		
SGRQ Total Score at Month 6	38.715 (± 22.3559)	37.368 (± 23.6868)		
Change from Baseline to Month 6	2.009 (± 13.4128)	-1.312 (± 11.6216)		

Notes:

[6] - Actual number analyzed:
Baseline: 168
Month 6: 169
Change: 168

[7] - Actual number analyzed:

Baseline: 104
Month 6: 106
Change: 104

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (AEs) were assessed at Baseline (Day 1) and all subsequent study visits through Month 28 (end of study).

Adverse event reporting additional description:

The analysis population consisted of the safety population, defined as all subjects who received at least 1 dose of either LAI+ MDR (multi-drug regimen) or MDR alone.

Subjects counted in all-cause mortality constitutes all deaths, regardless of whether or not there was an adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	LAI + Multi-drug Regimen

Reporting group description:

Subjects received LAI 590 mg QD in addition to their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines); LAI 590 mg QD, administered by inhaling drug product that had been aerosolized in an eFlow nebulizer over approximately 14 minutes

Reporting group title	Multi-Drug Regimen

Reporting group description:

Subjects received their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines)

Serious adverse events	LAI + Multi-drug Regimen	Multi-Drug Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 223 (20.18%)	23 / 112 (20.54%)	
number of deaths (all causes)	11	8	
number of deaths resulting from adverse events	6	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			

subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 223 (0.45%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial fistula			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 223 (3.14%)	3 / 112 (2.68%)	
occurrences causally related to treatment / all	4 / 12	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 223 (1.35%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	6 / 223 (2.69%)	5 / 112 (4.46%)	
occurrences causally related to treatment / all	4 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 223 (0.45%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			

subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maxillary sinus pseudocyst			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 223 (1.35%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary cavitation			
subjects affected / exposed	0 / 223 (0.00%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	2 / 223 (0.90%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 223 (0.90%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Computerised tomogram thorax abnormal			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 223 (0.00%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 223 (0.45%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			

subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Microvascular coronary artery disease			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypercapnic coma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			

subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	5 / 223 (2.24%)	3 / 112 (2.68%)	
occurrences causally related to treatment / all	2 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 223 (0.90%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 223 (0.90%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycetoma mycotic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterium avium complex infection			
subjects affected / exposed	1 / 223 (0.45%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	8 / 223 (3.59%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	1 / 9	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			

subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scedosporium infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	1 / 223 (0.45%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dehydration			
subjects affected / exposed	0 / 223 (0.00%)	1 / 112 (0.89%)	
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	LAI + Multi-drug Regimen	Multi-Drug Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	199 / 223 (89.24%)	72 / 112 (64.29%)	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 223 (8.07%)	3 / 112 (2.68%)	
occurrences (all)	19	3	

Nervous system disorders			
Headache			
subjects affected / exposed	22 / 223 (9.87%)	5 / 112 (4.46%)	
occurrences (all)	25	6	
Dizziness			
subjects affected / exposed	15 / 223 (6.73%)	3 / 112 (2.68%)	
occurrences (all)	16	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	36 / 223 (16.14%)	8 / 112 (7.14%)	
occurrences (all)	36	8	
Pyrexia			
subjects affected / exposed	17 / 223 (7.62%)	5 / 112 (4.46%)	
occurrences (all)	22	6	
Chest discomfort			
subjects affected / exposed	13 / 223 (5.83%)	3 / 112 (2.68%)	
occurrences (all)	13	4	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	18 / 223 (8.07%)	1 / 112 (0.89%)	
occurrences (all)	22	1	
Hypoacusis			
subjects affected / exposed	7 / 223 (3.14%)	6 / 112 (5.36%)	
occurrences (all)	7	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	29 / 223 (13.00%)	5 / 112 (4.46%)	
occurrences (all)	31	5	
Nausea			
subjects affected / exposed	25 / 223 (11.21%)	4 / 112 (3.57%)	
occurrences (all)	30	4	
Vomiting			
subjects affected / exposed	14 / 223 (6.28%)	3 / 112 (2.68%)	
occurrences (all)	17	4	
Constipation			

subjects affected / exposed	6 / 223 (2.69%)	6 / 112 (5.36%)	
occurrences (all)	6	6	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	104 / 223 (46.64%)	2 / 112 (1.79%)	
occurrences (all)	140	2	
Cough			
subjects affected / exposed	85 / 223 (38.12%)	17 / 112 (15.18%)	
occurrences (all)	111	20	
Dyspnoea			
subjects affected / exposed	47 / 223 (21.08%)	10 / 112 (8.93%)	
occurrences (all)	59	10	
Haemoptysis			
subjects affected / exposed	37 / 223 (16.59%)	14 / 112 (12.50%)	
occurrences (all)	48	17	
Oropharyngeal pain			
subjects affected / exposed	24 / 223 (10.76%)	2 / 112 (1.79%)	
occurrences (all)	30	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	15 / 223 (6.73%)	2 / 112 (1.79%)	
occurrences (all)	25	3	
Wheezing			
subjects affected / exposed	15 / 223 (6.73%)	3 / 112 (2.68%)	
occurrences (all)	16	4	
Sputum increased			
subjects affected / exposed	13 / 223 (5.83%)	1 / 112 (0.89%)	
occurrences (all)	15	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 223 (6.73%)	3 / 112 (2.68%)	
occurrences (all)	16	3	
Back pain			
subjects affected / exposed	13 / 223 (5.83%)	4 / 112 (3.57%)	
occurrences (all)	15	4	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	12 / 223 (5.38%)	8 / 112 (7.14%)	
occurrences (all)	15	10	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	15 / 223 (6.73%)	5 / 112 (4.46%)	
occurrences (all)	16	6	
Upper respiratory tract infection			
subjects affected / exposed	8 / 223 (3.59%)	7 / 112 (6.25%)	
occurrences (all)	9	10	
Pneumonia			
subjects affected / exposed	2 / 223 (0.90%)	6 / 112 (5.36%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 223 (6.73%)	8 / 112 (7.14%)	
occurrences (all)	17	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2015	Updates were made to include pharmacokinetic sampling in Japanese subjects, additional assessments, clarifications, administrative changes, removal of some lab tests.
11 June 2015	Update was done to modify endpoints and objectives, include additional objectives, study procedures, diagnostic testing, inclusion/exclusion criteria, additional analyses, clarification of inclusion/exclusion criteria, clarifications, define terms
22 February 2016	Administrative changes, removed some evaluations, updated procedures, updates to study design, revised inclusion/exclusion criteria, clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported