# 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 |
| Physician decision | 4 | 1 |
| Consent withdrawn by subject | 22 | 5 |
| Adverse event, non-fatal | 11 | 1 |
| Rescue Medication | 2 | - |
| Other not specified | 12 | - |
| Protocol deviation | 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: 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<br>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<br>Units: years | | | |
| arithmetic mean | 64.6 | 64.9 | |
| standard deviation | ± 9.59 | ± 10.16 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 165 | 68 | 233 |
| Male | 59 | 44 | 103 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 10 | 5 | 15 |
| Not Hispanic or Latino | 211 | 102 | 313 |
| Unknown or Not Reported | 3 | 5 | 8 |
| Race<br>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?<br>Units: Subjects | | | |
| Yes | 13 | 6 | 19 |
| No | 152 | 62 | 214 |
| Not female | 59 | 44 | 103 |
| If not childbearing potential, specify<br>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<br>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<br>Units: Subjects | | | |
| On treatment | 201 | 101 | 302 |
| Off treatment for at least 3 months | 23 | 11 | 34 |
| Smoking status (includes ecigarettes)<br>Units: Subjects | | | |
| Current smoker | 26 | 10 | 36 |
| Not a current smoker | 198 | 102 | 300 |
| Prior nebulized IV amikacin<br>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