9. DOCUMENTATION OF STATISTICAL METHODS

The following documents are provided in this section:

Statistical Analysis Plan	
Final Version 2.0	13 November 2018
Final Version 1.0	06 June 2017

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STATISTICAL ANALYSIS PLAN
PHASE III

VERSION: 2.0
DATE OF PLAN:

13-NOVEMBER-2018

BASED ON:

Protocol: INS-312 Amendment 3.1

CRF A.000139 WTT

STUDY DRUG:

amikacin liposome inhalation suspension

PROTOCOL NUMBER:

INS-312

STUDY TITLE:

AN OPEN-LABEL, SAFETY EXTENSION STUDY OF A MULTICENTER STUDY OF LIPOSOMAL AMIKACIN FOR INHALATION (ALIS) IN ADULT PATIENTS WITH NONTUBERCULOUS MYCOBACTERIAL (NTM) LUNG INFECTIONS CAUSED BY MYCOBACTERIUM AVIUM COMPLEX (MAC) THAT ARE REFRACTORY TO TREATMENT

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1. LIST OF ABBREVIATIONS

Sample text is provided in the table below. The list should be tailored to the specific requirements of the protocol and the terminology used in the analysis plan.

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALIS	Amikacin Liposome Inhalation Suspension
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CMH	Cochran Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DOB	Date of Birth
dy	Days
GCP	Good Clinical Practices
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mo	Months
N	Total Sample Size
PP	Per-Protocol Population
StdDev	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization
yr	Years

2. INTRODUCTION

This statistical analysis plan (SAP) describes the confirmatory analyses (referred to as the 'second analyses' in earlier versions) tabulations, summaries, and inferential analyses to evaluate to assess safety and tolerability of ALIS 590 mg QD added to a multidrug regimen (MDR) in subjects with NTM lung infections due to MAC. The initial analyses performed for the sub-part H submission to the FDA are described in version 3 (06Jun2017) version of the SAP.

The statistical analysis plan is based on:

- Protocol INS-312, Amendment 3.1, dated May 25, 2017
- ICH guidelines E6 and E9 (Statistical Principles for Clinical Trials)
- Discussions with the FDA

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used for the final confirmatory analyses of the safety and efficacy data for Study Protocol INS-312. The initial analyses performed for the FDA sub-part H submission are detailed in version 3, June 6, 2017 of the SAP.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

The use of the acronym ALIS (amikacin liposome inhalation suspension) is consistent feedback from the Food and Drug Administration (FDA) in June 2017 regarding the anticipated established name of the product. Previously, the product has been referred to as liposomal amikacin for inhalation (LAI) as an internal acronym as well as in publications. As such, the acronym LAI was used in the INS-312 protocol. This SAP using the ALIS acronym.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective is to evaluate long term safety and tolerability of ALIS (590 mg) administered once daily (QD) for up to 12 months in subjects who were refractory to standard multi-drug treatment and failed to convert in Study INS-212.

3.1.2. Secondary Objectives

These are the secondary objectives for the confirmatory analyses.

1. To evaluate the number of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 12/End of Treatment (EOT);
2. To evaluate the number of subjects achieving culture conversion by Month 6;
3. To evaluate the time to culture conversion;
4. To evaluate the change in the 6MWT distance at Month 6 and Month 12/EOT.

3.1.3. Exploratory Objectives

Exploratory objectives of the confirmatory analyses are:

1. To assess subject-reported symptoms of NTM and change from Baseline (Day1) in quality of life scores on the St. George's Respiratory Questionnaire (SGRQ) and quality of life scores on the SGRQ – Part II (Activity) at Month 6 and Month 12/EOT;
2. To assess the change from Baseline (Day 1) in the 3-level version of the EuroQol5-dimensional questionnaire (EQ-5D-3L) subject-reported health outcomes at Month 6 and Month 12/EOT.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoint is the frequency of treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal from study, treatment-emergent serious adverse events (SAEs), AEs of special interest, clinically significant abnormal laboratory test results, and vital signs measurements. The primary endpoint will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (ALIS added to a multi-drug regimen arm and a MDR alone).

3.2.2. Secondary Endpoints

The secondary efficacy endpoints are:

1. Proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures without relapse or recurrence) by Month 12/EOT.
2. Proportion of subjects achieving culture conversion by Month 6.
3. Time to culture conversion. The date of conversion is defined by the date of the first of at least 3 consecutive monthly culture specimens that are MAC negative.
4. The mean change from Baseline in 6MWT distance a Month 6 and Month 12/EOT

3.2.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

1. The mean change from Baseline at Month 6 and Month 12/EOT in the overall SGRQ and SGRQ – Part II (Activities of Daily Living) .
2. The mean change from Baseline at Month 6 and Month 12/EOT in the EQ-5D-3L.
3. Radiological changes in CT scan at EOT, within a sub-set of subjects

4. STUDY DESIGN

4.1. Summary of Study Design

Eligible subjects will have successfully completed their Month 6 visit in the INS-212 study. At or after all the INS-212 Month 6 visit assessments have been completed, the investigator will remind the subject of the potential opportunity to enroll in INS-312 at their scheduled Month 8 visit, to allow sufficient time for the subject to make an informed decision. At the scheduled Month 8 visit, eligible subjects will be confirmed to have not achieved the INS-212 protocol definition of culture conversion (3 consecutive negative sputum cultures) or to have experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred), as determined by the subjects' Day 1 through Month 6 sputum assessments in INS-212. The scheduled Month 8 visit will become the EOT visit. Subjects will be asked to provide written informed consent and will enroll directly from the INS-212 study at their EOT visit when all sputum results from Day 1 through Month 6 are known, and after having met all eligibility criteria.

All enrolled subjects will receive ALIS administered QD added to a multi-drug regimen for 12 months. All subjects will return 1 month after EOT for an off-ALIS treatment follow-up visit at the end of study (EOS) visit.

The study schematic is in Appendix X. The study time and events schedule is in Appendix Y.

4.2. Definition of Study Drugs

The study drug for Study INS-312 is amikacin sulfate is encapsulated in liposomes composed of DPPC and cholesterol (2:1 w:w lipid ratio) formulated as a suspension at a targeted concentration equivalent to 70 mg amikacin/mL in 10 mL of water for injection. The study drug is aerosolized in an eFlow nebulizer and inhaled over approximately 14 minutes.

4.3. Sample Size

There was no sample size determination as this study followed the INS-212 study; eligible subjects who consented after Month 6 and complete the EOT visit of Study INS-212 determined the sample size of this ongoing study.

4.4. Randomization

Not applicable.

4.5. Clinical Assessments

Efficacy assessments are sputum samples for MAC culturing, 6-minute walk test, SGRQ, and EQ-5D-3L. Safety assessments are adverse events, concomitant medications, clinical laboratory samples, CT scans (interpretation only), vital signs including pulse oximetry, and audiology tests. Other assessments collected include health care resource utilization (HCRU), and exploratory biomarkers (IL-6 and CRP). See the event schedule in Section 11.3 for details.

5. PLANNED ANALYSES

5.1. Initial Analyses

Analyses were performed to support a sub-part H accelerated approval application to the FDA. These analyses were performed on data cut at the time of the last subject's Month 6 visit in study INS-212 (07 July 2017).

The initial analyses are described in version 3.1 (06 June 2017) of the SAP.

No multiplicity adjustments are necessary for initial or the confirmatory analyses as there were no formal statistical hypothesis for the primary endpoints of this study for the initial or confirmatory analyses.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. Data Presentation Conventions

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums, and, if appropriate, by clinically relevant discretization's. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All data that meaningfully contribute to the objectives of the study will be included. Footnotes will specify the basis for the percentages. For counts of subjects, however, the denominator will generally be the number of subjects in the Safety population and treatment arm (based on treatment assignment in INS-212). All summary tables will be presented by treatment arm. A total summary column may be included in some summary tables wherever relevant.

Summaries of continuous variables that have some values recorded using approximate values (e.g., < or >) will use the numeric part of the value in calculations. Listings will present the data in its original format.

For summaries where rounding is required, rounding will be done to the nearest roundoff unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

Individual subject data obtained from the electronic case report forms (eCRFs), and any derived data will be presented by treatment, site, and subject in data listings.

An unscheduled visit can be used in the determination of baseline values, if it provides the last non-missing value prior to the first dose of the study drug. Post-baseline unscheduled visit data will be presented in the listings only (i.e., unscheduled visit data will not be summarized in tables). If subject has more than one data at a specific visit for any reason, average of the data at that visit will be considered in summary tables.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any other analyses performed will be considered post-hoc. Posthoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® version 9.4 or higher. Tables, listings, and figures will be created in rich text format.

All tables are broken down by region, country, and site including the overall groups within each. The first group will always be the overall group. The definition of regions and order of presentation is in Table 2. Countries will be ordered by the number of enrolled subjects within the country and presented in descending order (ie, country with the most subjects first). Sites will be ordered by the number of enrolled subjects within the sites and presented in descending order (ie, site with the most subjects first).

Table 2: Study Regions

Presentation Order	Region Name	Region Abbreviation	Countries in Region
1	All	All	Austria, Germany, Spain, France, Great Britain, Italy, Netherlands, Poland, Israel, Japan, USA, Canada, Australia, and New Zealand
2	North America	N.Amer	USA and Canada
3	Japan	JPN	Japan
4	Europe	EU	Austria, Germany, Spain, France, Great Britain, Italy, Netherlands, Poland, Israel, and Sweden
5	Asia	Asia (Excluding Japan)	South Korea, Thailand
6	Oceania	Oceania	Australia and New Zealand

6.2. Analysis Populations

6.2.1. Safety Population

The safety population is the set of subjects who received at least 1 dose of ALIS.

6.3. Baseline Definition

Any non-missing value from any procedure at a subjects EOT visit in study INS-212 will be denoted as their baseline value. If that result from the aforementioned visit is missing, then the non-missing value at the subsequent visit in the INS-312 study.

6.4. Derived and Transformed Data

6.4.1. Sustained Conversion

For subjects who convert (ie, 3-consecutive negative monthly MAC cultures), the conversion will be considered ‘sustained’ if there are no positive solid media and no more than 2 consecutive positive monthly broth MAC cultures from conversion through End of Treatment.

6.4.2. Baseline Age

Use subject’s age as reported on the CRF.

6.4.3. Study Day

Study day, the number of days from enrollment, is derived using the following formula:

STUDYDAY = (assessment– enrollment date) + (assessment >= enrollment date);

there is no study day 0.

6.4.4. Study Month

Study month, the number of months from enrollment is derived using the following formula:

STUDYMON = STUDYDAY/30.

6.4.5. Duration

Duration is the time between two dates and may be expressed in days, months, or years. The formulae for deriving duration are:

- Duration (days) = end – start dates + 1
- Duration (months) = (duration [days])/30.4
- Duration (years) = (duration [days])/365.25

6.4.5.1. Total Duration

Total duration is the duration within a reporting group (eg, SOC). Total duration is derived with the subject and is the sum of all durations in the reporting group.

6.4.5.2. Maximum Duration

Maximum duration is the longest duration within a reporting group (eg, SOC).

6.4.5.3. Mean Duration

Mean duration is the average duration within a reporting group (eg, SOC), derived as the total duration divided by the number of events in the reporting group.

6.4.6. Change-from-baseline

Change-from-baseline is calculated as (post-baseline result – baseline result).

Percent change-from-baseline is calculated as (100 * change-from-baseline/baseline result).

If either the baseline or the post-baseline result is missing, the change-from-baseline and percentage change-from-baseline are also missing.

6.4.7. ALIS Treatment

Study drug (ALIS) was the only study treatment provided by the sponsor. Therefore, compliance can only be determined for ALIS and then compliance can only be determined based on vial counts.

The MDR treatments are captured in the concomitant medication log, but compliance with dosing was not tracked during the study. However, since subjects came to the study on MDR and continued MDR treatment through the study and after leaving the study, duration of MDR is not informative.

6.4.7.1. Duration of ALIS

Duration of ALIS will be derived as the last dose – first dose + 1 as captured on the CRF.

6.4.7.2. Compliance with ALIS

Because ALIS is a once a day dosing, prescribed number of doses is the same as the duration. Therefore, compliance with ALIS will be derived as the number of vials taken / duration of ALIS. Protocol allowed ALIS treatment interruptions, were not captured in a manner that these interruptions can be accounted for in compliance.

6.4.8. CTC Grading of Audiology Results

Hearing loss will be graded based on the CTC grading criteria in Table 3 .

Table 3: Hearing Loss CTC Grade

Grade	Criteria
1	Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear.
2	Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear.
3	Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated.
4	Decrease in hearing to profound bilateral loss (absolute threshold >80 dB hearing loss at 2 kHz and above); non-serviceable hearing.

The baseline hearing test is the threshold for deriving the grade. Subjects who do not meet any of the above CTC grades will have a CTC grade of zero (0).

6.4.9. Visit Windows

Nominal visit windows will be used for all visits, except for EOT and EOS visits. Because EOT and EOS visits are conducted in place of the planned visit for subjects who prematurely end treatment or study participation, these visits also need to be mapped to the coincident visit.

For example, a subject discontinues treatment at the Month 4 visit. The site will conduct the EOT visit at Month 4 rather than the Month 4 visit, but for analysis purposes this visit should be used for the Month 4 summary as well as the EOT summary. Similarly, for the EOS visit. Thus, should it be appropriate, the EOT and EOS visit need to be mapped to the corresponding visit. Should the EOT or EOS visit map to a time that doesn't coincide with a scheduled visit, it will not be mapped.

Subjects who prematurely discontinue from the study, may not have an EOT visit. In this case the EOS visit will also be the EOT visit and should be mapped accordingly.

Table 4: Visit Windows (Days)

Visit Name	Visit Number	Target Anchor	Relative Target Day	Visit Window
Baseline	1	Last visit from Study INS-212	1	-2 to 1
Month 1	2		30	23 to 37
Month 2	3		60	53 to 67
Month 3	4		90	83 to 97
Month 4	5		120	113 to 127
Month 5	6		150	143 to 157

Visit Name	Visit Number	Target Anchor	Relative Target Day	Visit Window
Month 6	7		180	173 to 187
Month 7	8		210	203 to 217
Month 8	9		240	233 to 247
Month 9	10		270	263 to 277
Month 10	11		300	293 to 307
Month 11	12		330	323 to 337
Month 12 (EOT)	13		365	353 to 367
Month 13 (EOS)	14		420	413 to 427

6.4.10. Multiple Assessments

Sputum samples will be captured daily starting two days before each visit. Thus, each visit will have up to three sputum samples. For the determination of culture conversion, should any sputum samples at that visit be MAC culture positive, that visit is considered positive for MAC. When determining if a subject had 3-consecutive monthly negative sputum cultures, only schedule monthly samples will be used. However, subjects with a positive unscheduled sputum sample culture among the 3-consecutive monthly negative sputum cultures will not be deemed as achieving culture conversion.

For the determination of sustained culture conversion, if a subject has any positive solid media culture whether scheduled or unscheduled after conversion or with at least 3 consecutive positive scheduled monthly liquid media cultures, that subject will not have achieved sustained culture conversion.

6.5. Handling of Missing Data

6.5.1. Missing Efficacy Endpoints

6.5.1.1. Conversion

A sputum culture will be considered missing at the visit only if there are no sputum samples at that visit to culture. Visits with missing sputum cultures prior to subject converting will be considered as positive cultures. This results in the most conservative outcome, ie, most conversion failures.

6.5.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Medications with partial start and stop dates may be considered as a prior, concomitant, or both. If time is needed for analysis purpose, all missing or partial times will be replaced by 00:00 (HH:MM) for start times and 23:59 for stop times using 24-hour clock.

The following algorithm will be applied to missing and incomplete start and stop dates, stop dates should be imputed before start dates:

Concomitant Medication Stop Dates:

- If the stop date is completely missing, the stop date year is missing, or the medication is ongoing, then set the stop date to the last available subject visit date.
- If the day portion of the stop date is missing, then set the day to the last day of the month, if available otherwise set the day to the 31st.
- If the month portion of the stop date is missing, then set the month to December ('DEC').

Concomitant Medication Start Dates:

- If the imputed stop date is after the first dose of study drug (ALIS), then impute the missing portion of the start date as follows:
  - If only the day portion of the start date is missing, then the day will be set to the first ('01') of the month.
  - If both the day and month portions of the start date are missing, then the day and month will be set to the first ('01') of the month and the month will be set to January ('JAN').
  - If the start date is completely missing, then the start date will be imputed first day of the same year (ie, 01Jan) as the stop date.
- If the imputed stop date is on or before the first dose of study drug (ALIS) or completely missing (ie, ongoing), then impute the missing portion of the start date as follows:
  - If the day portion of the stop date is missing, then set the day to the first ('01').
  - If the month portion of the stop date is missing, then set the month to January ('JAN').
  - If the year is missing, then set the year to the screening visit year.

After start dates have been imputed, check that the imputed start date is on or before the imputed stop date. If imputed start date is after the imputed stop date, set the imputed start date to the imputed stop date.

6.5.3. Missing Start and Stop Dates for Adverse Events

For AEs, missing or incomplete onset or end dates will be imputed such that the AE is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) unless the partial onset date or end date, indicates differently. If time is needed for analysis purpose, all missing or partial times will be replaced by 00:00 (HH:MM) for start times and 23:59 for stop times using 24-hour clock.

The following algorithm will be applied to missing and incomplete onset and end dates, end dates should be imputed before onset dates:

Adverse Event End Dates

- If the end date is completely missing or the year portion of end date is missing (even if day or month are present), or the AE is ongoing, then set the end date to the last available subject visit date.

- If the month portion of the end date is missing and the year is present, then set the month to December.
- If only the day portion of the end date is missing, then set the day to the last day of the month.

Adverse Event Onset Dates:

- If the imputed end date is on or after the first dose of study drug (ALIS), then impute the missing portion of the onset date as follows:
  - If only the day portion of the onset date is missing, and the month and year are the same as the month and year of the first dose of ALIS; otherwise the missing day will be set to the first ('01') of the month.
  - If month portion of the onset date is missing and the year is present, and the year is the same year as the first dose of ALIS; otherwise set the month to January ('JAN').
  - If the onset date is completely missing or the year portion of onset date is missing, the onset date will be imputed to the date of first dose of ALIS.
- If the imputed end date is before the first dose of study drug (ALIS), then impute the missing portion of the onset date as follows:
  - If only the day portion of the end date is missing, then set the day to the first ('01').
  - If the month portion of the onset date is missing and the year is present, then set the month to January ('JAN').
  - If the onset date is completely missing or the year portion of onset date is missing, then set the year to the end date year.
- After onset dates have been imputed, check that the imputed onset date is on or before the imputed end date. If imputed onset date is after the imputed end date, set the imputed onset date to the imputed end date.

7. STUDY POPULATION

7.1. Subjects Disposition

All disposition tables will present the data by INS-212 randomized treatment and total groups as columns in the table. all percentages on disposition tables will use the Safety population as the denominator.

7.1.1. End of Study Disposition

End of Study Disposition - Overall

The end of study disposition overall table will present the number of subjects that were enrolled (ie, screened), safety population, completed study, discontinued from study, and reasons for discontinuation from study. Percentages will only be presented for completed and discontinued study, and reasons for discontinuation.

End of Study Disposition – by Visit

The end of study disposition table by visit will present the number of subjects who discontinued at that visit and the reasons for discontinuation.

7.1.2. End of Treatment Disposition

End of treatment disposition will present the number and percentage of subjects who completed and discontinued treatment for any reason, and the reasons for treatment discontinuation (death, adverse event, protocol deviation, noncompliance with study drug, lack of efficacy, withdrawal by subject, lost to follow-up, physician decision, site terminated by sponsor, study terminated by sponsor, rescue medication, and other). Except for completed, these reasons will appear on both overall and by visit end of treatment disposition tables. The reasons for discontinuation should be presented in descending order of the total column subject count.

End of Treatment Disposition - Overall

The end of treatment disposition overall table will present the number of subjects that completed treatment, discontinued treatment, and reasons for treatment discontinuation.

End of treatment Disposition – by Visit

The end of treatment disposition table by visit will present the number of subjects who discontinued at that visit and the reasons for discontinuation. Percentages on this table will use the Safety population as the denominator.

7.2. Screen Failures

Not applicable.

7.3. Protocol Deviations

The protocol deviation tables will present the Safety population. The number and percentage of subjects will be presented.

7.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be tabulated or summarized as appropriate with treatment arm (based on study INS-212) and total columns for the safety population.

Demographic parameters are age, race, ethnicity, sex, and childbearing potential (females only).

Baseline characteristics are contraception (childbearing females only), St. George's Respiratory Questionnaire (SGRQ) total score, SGRQ symptoms score, SGRQ activity score, SGRQ impacts score, SGRQ question 'how do you describe your current health?', SGRQ question 'what best describes your respiratory problems affect you?', EQ-5D-3L visual analog score (VAS), EQ-5D-3L mobility score, EQ-5D-3L self-care score, EQ-5D-3L usual activities score, EQ-5D-3L pain/discomfort score, EQ-5D-3L anxiety/depression score, CRP (biomarker), IL-6 (biomarker), 6-minute walk test (6MWT) distance, 6MWT supplemental oxygen use, 6MWT early termination, 6MWT remaining time (for early termination subjects only), 6MWT distribution of the number of rests, 6MWT vital signs (pre-test, post-test, and change-from-pre-test in heart rate, respiratory rate, systolic and diastolic blood pressures, and oxygen saturation), 6MWT dyspnea score (pre-test, post-test, and change-from-pre-test), 6MWT distribution of dyspnea scores (pre-test and post-test), 6MWT fatigue score (pre-test, post-test, and change-from-pre-test), 6MWT distribution of fatigue scores (pre-test and post-test), audiology tests (decibels at 250, 500, 1000, 2000, 4000, and 8000 Hz in each ear), visit vital signs (height, weight, body mass index [BMI], temperature, pulse rate, respiratory rate, systolic and diastolic blood pressures, and oxygen saturation).

Age, SGRQ scores (total, symptoms, activity, impacts), EQ-5D-3L scores (VAS, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), biomarkers (CRP, IL-6), 6MWT (distance, time remaining, vital signs, dyspnea score, and fatigue score), audiology (for each ear within each frequency), and vital signs will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum).

Age will also be categorized into groups 18-45, 46-64, 65+, 75+, and 85+. The groups 65+, 75+ and 85+ are not mutually exclusive, thus the 65+ group will contain all subjects in the 75+ and 85+ groups and the 75+ group will include the 85+ group.

Age groups, race, ethnicity, sex, childbearing potential (females only), contraception (childbearing females only), SGRQ question 'how do you describe your current health?', SGRQ question 'what best describes your respiratory problems affect you?', 6MWT (supplemental oxygen use, early termination, number of rests, dyspnea score, and fatigue score), and PFT prior bronchodilator use status will be tabulated presenting the number and percentage of subjects in each category.

Subject reporting multiple races will appear in each race they reported. Thus, the total number of subjects with the race groups may exceed the total number of subjects in that column. A group of 'not recorded' will be included with the race groups to account for subjects who declined reporting their race.

7.5. Medical History and Medical Conditions Present at Entry

Medical history will be tabulated by treatment and total for the safety population. The number and percentage of subjects will be presented for subjects reporting at least one medical history and by body system/organ class and preferred term within body system organ class. Medical history is coded using MedDRA 19.1.

7.6. Prior Medication History and Medications Present at Baseline

Prior and concomitant medications are coded using the Who Drug Sept16 dictionary. Prior medications, prior MDR (indicated on the CRF) for NTM-MAC, and concomitant medications are presented in separate tables. The number and percentage of subjects reporting at least one medication and by anatomical therapeutic class level 4 (ATC4) and preferred term within ATC4 will be presented.

The number and regimen of prior MDR for NTM-MAC at baseline will be tabulated. This table was provided with the initial analyses (14.1.9.1). Multi-drug regimen medications are classified into ethambutol, macrolide, rifamycin, or other as follows:

Table 5: Multi-drug Regimen Classification

Classification	Medications
Ethambutol	Ethambutol, Ethambutol Di1hydrochloride, Myrin Plus[1]
Macrolide	Azithromycin, Clarithromycin, Erythromycin, Roxithromycin
Rifamycin	Rifampicin, Rifabutin, Rifamycin, Rifinah, Rifater, Myrin Plus[1]
Other	Any medication flagged as part of MDR that doesn't fit the above classifications.

[1] Myrin Plus is a combination product containing an ethambutol and rifamycin.

8. EFFICACY

8.1. General Considerations

All analyses of efficacy endpoints will be sorted by the patient's treatment in study INS-212 and will use the Safety Population.

8.2. Statement of the Null and Alternate Hypotheses

Not applicable

8.3. Subgroup Analyses

Not applicable.

8.4. Multiple Comparisons and Multiplicity

As described in section 5.1, multiplicity adjustments are not necessary for initial or the confirmatory analyses as there were no formal statistical hypothesis for the primary endpoints of this study for the initial or confirmatory analyses.

8.5. Analysis of the Primary Efficacy Endpoint

8.5.1. Primary Efficacy Analysis

There is no primary efficacy endpoint for Study INS-312; all efficacy endpoints were secondary or exploratory.

8.5.2. Sensitivity Analyses of the Primary Efficacy Results

Not applicable.

8.6. Analysis of the Secondary Efficacy Endpoints

8.6.1. Culture Conversion

Culture conversion through 6 months and 12 months of treatment will be analyzed across all groups and within groups.

8.6.2. Time to Culture Conversion

The traditional failure time analysis of culture conversion will be based solely on the INS-312 Safety population.

Kaplan-Meier estimates of the time-to-conversion curves will be produced with and without stratification by the prior 2 treatment groups (from INS-212). Median time to conversion together with the 25th and 75th percentiles and their associated 95% CIs will be presented by treatment group and overall. Kaplan-Meier curve for time to Culture Conversion will be provided in a figure.

The following lines provide sample SAS code for the Kaplan-Meier estimates.

```
PROC LIFETEST DATA=input_data METHOD=KM;
        TIME DAYS*CENSOR(1);
        STRATA TRT / NOTEST;
RUN;
```

For the survival curve, DAYS is the number of days from baseline to culture conversion; TRT is the treatment and CENSOR is an indicator variable that indicates whether the subject was classified as having converted (CENSOR = 0) or not having converted (CENSOR = 1).

8.6.3. Six-minute Walk Test

The 6MWT is performed at baseline, Month 6, and Month 12/EOT visits.

The 6MWT distance actual, baseline and change-from-baseline will be summarized by visit based on those subjects within the ITT population who have data at that visit. At each visit the baseline summary will reflect those subjects who provided data at that visit.

8.7. Analysis of Exploratory Efficacy Endpoints

The St George's Respiratory Questionnaire and the EQ-5D-3L questionnaire comprise the exploratory endpoints for confirmatory analysis. This confirmatory analysis of exploratory endpoints will not compare prior INS-212 study treatments. The Safety population will be used for this analysis.

8.7.1. St. George's Respiratory Questionnaire

The SGRQ is captured at baseline, Month 6, Month 12/EOT, and EOS.

The SGRQ scores (total, symptoms, activities, impacts) actual, baseline and change-from-baseline will be summarized by visit based on those subjects who have data at that visit. At each visit the baseline summary will reflect those subjects who provided data at that visit.

8.7.2. EQ-5D-3L

The EQ-5D-3L is captured at baseline, Month 6, Month 12/EOT, and EOS.

The EQ-5E-3L scores (VAS, Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) actual, baseline and change-from-baseline will be summarized by visit based on those subjects who have data at that visit. At each visit the baseline summary will reflect those subjects who provided data at that visit.

8.7.3. Health Care Resource Utilization

Health care resource utilization (HCRU) is a questionnaire based on subject recall asking about the use of hospitalizations, emergency room (ER) visits, doctor visits, and other information. The questionnaire was administered at baseline, Month 1, Month 3, Month 6, Month 9, Month 12/EOT visits.

All summaries of HCRU data will be done by visit.

For subjects who have more than one hospitalization, the duration of hospitalizations for the HCRU summaries is the sum of all hospitalizations durations for the subject. Durations for

unplanned hospitalizations, planned hospitalization, ICU Admissions, hospitalizations due to NTM, and ICU admissions due to NTM will be derived in a similar manner for the summaries.

Hospitalizations

For each hospitalization since the last study visit subjects were asked the following:

- Since your last visit, were you admitted to the hospital?
- Was this a planned hospitalization?
- Dates of admission and release.
- Was the hospital admission related to NTM?
- If you were admitted to the hospital, did it result in being admitted to the ICU?
  - If yes, dates of ICU admission and release.

The number and percentage of subjects within each treatment and total will be presented for the following:

- Since your last visit, were you admitted to the hospital? (yes/no)
- Number of hospitalizations
- Number of unplanned hospitalizations
- Number of planned hospitalizations
- ICU admission (yes/no)
  - Number of ICU admissions
- Admission related to NTM (yes/no)
  - Number of NTM hospitalizations
  - Number of NTM ICU admissions

Summary statistics (n, mean, standard deviation, median, minimum, maximum) will be presented for the following:

- Duration of all hospitalizations
- Duration of unplanned hospitalizations
- Duration of planned hospitalizations
- Duration of ICU admissions
- Duration of hospitalizations due to NTM
- Duration of ICU admissions due to NTM

Emergency Room Visits

For each ER visit subjects were asked the following:

- Since your last visit, did you visit the ER?

  - ER Visit Date
  - Did your visit to the ER result in being admitted to the hospital?

The number and percentage of subject responses (yes/no) to the questions 'since your last visit, did you visit the ER' and 'did your visit to the ER result in being admitted to the hospital' will be presented.

Doctor Visits

Regarding doctor visits subjects were asked the following:

- Since your last visit, how many times did you visit a doctor (other than your study related visits)?
- Were doctor's visits related to NTM?
- Reason for Doctor Visits other than NTM

The distribution of the number of times subjects visited the doctor (0, 1, 2, >2) and the question "were doctor's visits related to NTM" (yes/no) will be presented indicating the number and percentage of subjects at each level by treatment and total.

Other

For the 'other' subjects were asked the following:

- Are you working?
  - If Yes, how many days did you miss work since your last visit?
  - If Yes, was missed work related to NTM?
- Have you been placed on disability/social security related to you having NTM since your last visit?
- How many hours of sleep (on average) have you been getting since your last visit?
- Have you refrained from certain family/social/work activities based on the symptoms associated with NTM since your last visit?
- Have you added back into your daily routine any previously discontinued activities since your last visit?
  - If Yes, please describe

The number and percentage of subjects within each treatment and total will be presented for the following:

- Response (yes/no) to
  - Placed on disability/social security
  - Refrained from family/social/work activities
  - Added routine activities previously discontinued
  - Working

    - If yes, were
        - work days missed
        - work days missed due to NTM
- Distributions of
    - Number of work days missed
    - Number of work days missed due to NTM

Summary statistics (n, mean, standard deviation, median, minimum, maximum) will be presented for the following:

- Average number of hours slept per day
- Number of work days missed
- Number of work days missed due to NTM

8.8. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

Not applicable

9. SAFETY AND TOLERABILITY

Safety and tolerability summaries will present data for all subjects treated (ie, Safety Population) overall and by the prior INS-212 study treatment the subject received.

The analyses of safety and tolerability data include an overall summary of adverse events (AE), AE preferred terms by body/organ system, drug exposure (duration of treatment), ALIS treatment compliance, concomitant medications, clinical laboratory results, vital signs, , and audiology tests. Adverse events summaries are broken into the 2 groups, treatment-emergent, and post-treatment.

Unless otherwise specified, percentages for all safety tables will be based on the number of subjects in the Safety Population for the total column and treated in the treatment columns.

9.1. Overall Summary of Adverse Events

9.1.1. Overall Summary of Treatment-emergent Adverse Events

The overall summary of AEs will present the number and percentage of subjects meeting the following criteria:

1. At least one TEAE
2. At least one serious TEAE
3. At least one TEAE leading to study drug withdrawn
4. At least one TEAE leading to multi-drug regimen for NTM withdrawn
5. At least one TEAE leading to study drug and MDR multi-drug regimen for NTM withdrawn
6. At least one Serious TEAE leading to study drug withdrawn
7. At least one TEAE leading to death
8. At least one TEAE which is Pulmonary Exacerbation
9. At least one Serious TEAE which is Pulmonary Exacerbation
10. At least one TEAE which is a cough event
11. At least one TEAE related to nebulizer device used for study drug administration
12. Maximum Reported Severity
    a. Grade 1 (mild)
    b. Grade 2 (moderate)
    c. Grade 3 (severe)
    d. Grade 4 (life threatening)
    e. Grade 5 (death)
13. Closest Relationship to Study Drug
    a. Related (Definitely, Possibly, or Probably Related)
    b. Not related
14. Other suspect therapy
    a. None
    b. Azithromycin
    c. Clarithromycin
    d. Ethambutol
    e. Rifampin

f. Rifabutin
g. Other

Subjects will be counted only once in Items 1 through 13. Subjects will be counted at the highest severity reported in Item 12. Subjects will be counted at the closet relationship to study drug (ALIS) in Item 13. In Item 14 subjects will be counted only once for each suspect therapy reported; if any suspect therapy is reported, the subject will not be counted in the 'none' category.

9.1.2. Overall Summary of Adverse Events Resulting in Hospitalization

For AEs that resulted in hospitalization, the overall summary will present the following information:

1. Number and percent
   a. Of subjects with at least one hospitalization AE
   b. Number of hospitalizations per subject

9.1.3. Adverse Events of Special Interest

Table 6 lists the adverse events of special interest (AESI) by AESI group, system organ class and preferred term.

Table 6: Adverse Events of Special Interest

AESI Group	System organ class	Preferred term
Neuromuscular	Musculoskeletal and connective tissue disorders	Muscular weakness
	Nervous system disorders	Balance disorder
		Neurotoxcity
		Neuropathy peripheral
		Peripheral sensory neuropathy
Nephrotoxicity	Renal and urinary disorders	Haematuria
		Proteinuria
		Renal failure
		Azotaemia
		Bilirubinuria
		Leukocyturia
		Nitrituria
		Renal impairment
	Investigations	Blood creatinine increased
		Blood urine present
		Creatinine renal clearance increased

AESI Group	System organ class	Preferred term
		Glomerular filtration rate abnormal
		Glomerular filtration rate decreased
		Red blood cells urine positive
		Urine bilirubin increased
		Urinary casts present
Ototoxicity	Ear and labyrinth disorders	Deafness
		Deafness bilateral
		Deafness neurosensory
		Deafness unilateral
		Hearing impaired
		Hypoacusis
		Tinnitus
		Vertigo
	Nervous system disorders	Balance disorder
		Dizziness
		Presyncope
Alveolitis Allergic	Respiratory, thoracic and mediastinal disorders	Alveolitis allergic
		Eosinophilic pneumonia
		Interstitial lung disease
		Pneumonitis
Bronchospasm	Respiratory, thoracic and mediastinal disorders	Asthma
		Bronchial disorder
		Bronchial hyperreactivity
		Bronchospasm
		Dyspnoea
		Dyspnoea exertional
		Prolonged expiration
		Tachypnoea
		Throat tightness
		Wheezing
	Investigations	Forced expiratory volume decreased
		Pulmonary function test decreased
Infective Exacerbation of	Respiratory, thoracic and	Chronic obstructive pulmonary disease

AESI Group	System organ class	Preferred term
Underlying Disease	mediastinal disorders	
	Infections and infestations	Infective exacerbation of bronchiectasis
		Infective exacerbation of chronic obstructive airways disease
		Infective pulmonary exacerbation of cystic fibrosis
		Infective exacerbation of chronic obstructive airways disease
Haemoptysis	Respiratory, thoracic and mediastinal disorders	Haemoptysis
Other Respiratory	Respiratory, thoracic and mediastinal disorders	All preferred terms not mentioned in another group
Exacerbation of COPD	Infections and infestations	Infective exacerbation of chronic obstructive airways disease
	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Adverse events will be presented for the treatment-emergent, and post-treatment periods. Treatment-emergent period is the day of first dose of ALIS through 28 days after the last dose of study medication, end of treatment visit, or end of study visit, whichever is earlier.

9.2.1. Tabulations of Adverse Events

Adverse events will be tabulated presenting the incidence and percentage of subjects along with the number of events by and across prior INS-212 treatment arms. Incidence of an adverse event is the number of subjects reporting the adverse event at least once. The denominator for the percentage is the number of subjects receiving the treatment within the analysis population for the by treatment arm tabulation and total number of subjects enrolled and receiving treatment for the total.

Incidence, percentage, and number of AEs will be reported for subjects reporting at least one AE, within the system/organ class (SOC), and by preferred term within the SOC. Adverse tabulations will be generated for the following:

- Pre-treatment AEs
    - All
    - Serious
        - All
        - Fatal

        - Leading to hospitalization
- Treatment-Emergent
    - AEs
        - All
        - Common (>=5%)
        - Related to study treatment
        - Leading to withdrawal from study
        - Leading to withdrawal of study treatment
        - Leading to withdrawal of ALIS
        - Leading to withdrawal of MDR
        - Leading to withdrawal of both ALIS and MDR
        - Resulting in study drug interruption
        - Resulting in interruption of ALIS
        - Resulting in interruption of MDR
        - Resulting in interruption of both ALIS and MDR
        - By maximum toxicity grade
        - By relationship to ALIS
        - Related to nebulizer
    - Serious AEs
        - All
        - Common (>=5%)
        - Related to study treatment
        - Leading to withdrawal from study
        - Leading to withdrawal of study treatment
        - Leading to withdrawal of ALIS
        - Leading to withdrawal of MDR
        - Leading to withdrawal of both ALIS and MDR
        - Resulting in study drug interruption
        - Resulting in interruption of ALIS
        - Resulting in interruption of MDR
        - Resulting in interruption of both ALIS and MDR
        - By maximum toxicity grade

        - By relationship to ALIS
        - Resulting in hospitalization
        - Related to nebulizer
        - Fatal
    - AEs of Special Interest
        - All
        - Common (>=5%)
        - Related to study treatment
        - Leading to withdrawal from study
        - Leading to withdrawal of study treatment
        - Leading to withdrawal of LAI
        - Leading to withdrawal of MDR
        - Leading to withdrawal of both LAI and MDR
        - Resulting in study drug interruption
        - Resulting in interruption of LAI
        - Resulting in interruption of MDR
        - Resulting in interruption of both LAI and MDR
        - By maximum toxicity grade
        - By relationship to LAI
        - Related to nebulizer
    - Serious AEs of Special Interest
        - All
        - Common (>=5%)
        - Related to study treatment
        - Leading to withdrawal from study
        - Leading to withdrawal of study treatment
        - Leading to withdrawal of LAI
        - Leading to withdrawal of MDR
        - Leading to withdrawal of both LAI and MDR
        - Resulting in study drug interruption
        - Resulting in interruption of LAI
        - Resulting in interruption of MDR

        - Resulting in interruption of both LAI and MDR
        - By maximum toxicity grade
        - By relationship to LAI
        - Related to nebulizer
- Post-Treatment AEs
    - All
    - Serious
        - All
        - Fatal
        - Leading to hospitalization

For related AEs tabulations and for adverse event tabulations by relationship to ALIS, an AE will be considered related if it is 'definitely', 'probably', or 'possibly' as indicated on the CRF. The related AEs tabulations will present only those AEs deemed related. The adverse event tabulations by relationship to ALIS will present a column for related and another for not related AEs.

Tabulations by maximum toxicity grade will report subjects only once at the highest toxicity grade reported with the summary level (eg, SOC, preferred term).

9.2.2. Summaries of Duration of Adverse Events

The duration of serious AEs, serious AEs resulting in hospitalization, and AEs in the 'respiratory, thoracic and mediastinal disorders' body system will be summarized.

The duration of AEs will be summarized (n, mean, standard deviation, median, minimum, and maximum) for each system/organ class and preferred term within the system organ class. The total duration is the sum of the duration for all AEs within a subject at the SOC level, for the SOC summaries and within the preferred term for preferred term summary. The maximum duration is the maximum of the durations for all AEs within a subject at the SOC level, for the SOC summaries, and within preferred term for the preferred term summary. The mean duration is the mean of the durations for all AEs within a subject at the SOC level, for the SOC summaries, and within preferred term for the preferred term summary.

The summary table of AE durations will also include a tabulation of the number of events per subject reported in the summary level (ie, SOC, preferred term level).

9.3. Total Duration and Compliance of ALIS Therapy

Duration and compliance summaries (ALIS only) will be presented by baseline to Month 6, Baseline to EOT, and Month 6 to EOT study periods. Duration of treatment and compliance will be summarized (n, mean, standard deviation, median, minimum, and maximum). Compliance will be categorized (>120%, 80-120%, <80%) and tabulated (number and percentage of subjects).

9.4. Concomitant and Other Medications

Concomitant medications will be coded using the WHO Drug Sept2016 dictionary. Tabulations will be done for the safety, populations. The number and percentage of subjects reporting the medication will be presented for subjects using at least 1 medication, at least one medication at the Anatomical Therapeutic Class Level 4 (ATC4) level, and by preferred term within ATC4.

9.5. Routine Laboratory Data

All clinical laboratory data summaries and tabulations will be based on the safety population.

At each visit, only those subjects providing data at the visit will appear on the tables.

The actual, baseline and change-from-baseline of the clinical laboratory results (blood chemistry and hematology) will be summarized (n, mean, standard deviation, median, minimum, and maximum) by visit for each prior treatment and total groups. At each visit the baseline summary will reflect those subjects who provided data at that visit.

Shifts-from-baseline-to-visit in categorization of result by normal ranges (low, normal, high, total) will be tabulated clinical laboratory results (blood chemistry and hematology) presenting the number and percentage of subjects in each cell. These shift tables will also be presented for clinically significant labs.

9.6. Vital Signs

All vital signs data summaries and tabulations will be based on the safety population.

At each visit, only those subjects providing data at the visit will appear on the tables.

The actual, baseline and change-from-baseline of the vital signs will be summarized (n, mean, standard deviation, median, minimum, and maximum) by visit and timepoint (pre-dose and post-dose) for each prior treatment and overall. At each visit the baseline summary will reflect those subjects who provided data at that visit.

9.7. Audiology Tests

All audiology testing data summaries and tabulations will be based on the safety population.

At each visit, only those subjects providing data at the visit will appear on the tables.

The actual, baseline and change-from-baseline audiology test results at each will be summarized (n, mean, standard deviation, median, minimum, and maximum) by visit, frequency, and ear for each prior treatment and overall. At each visit the baseline summary will reflect those subjects who provided data at that visit.

The audiology results will be tabulated (number and percentage of subjects) by CTC grade (0, 1, 2, 3, 4) and total for either, left, and right ears within treatment and total groups.

9.8. Physical Examination

The site was instructed to report any changes found during the physical exam as AEs. There is no summary for physical examination.

10. REFERENCES

1. John L. Hankinson, Steven M. Kawut, Eyal Shahar, Lewis J. Smith, Karen Hinckley Stukovsky and R. Graham Barr. Study of Atherosclerosis (MESA) Lung Study Reference Values in a Multiethnic Sample of Adults : The Multi-Ethnic Performance of American Thoracic Society-Recommended Spirometry Chest 2010;137; 138-145; Prepublished online September 9, 2009

11. APPENDIX

11.1. Table of Contents for Data Display Specifications

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14.3.1.6.3	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO WITHDRAWAL OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.1.6.4	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO WITHDRAWAL OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.1.7.1	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS RESULTING IN INTERRUPTION OF STUDY TREATMENT	SAFETY POPULATION	
14.3.1.7.2	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS RESULTING IN INTERRUPTION OF LAI	SAFETY POPULATION	
14.3.1.7.3	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS RESULTING IN INTERRUPTION OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.1.7.4	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS RESULTING IN INTERRUPTION OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.1.8	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS BY MAXIMUM TOXICITY GRADE	SAFETY POPULATION	
14.3.1.9	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS BY RELATIONSHIP TO LAI	SAFETY POPULATION	
14.3.1.10	SUMMARY OF DURATION OF TREATMENT-	SAFETY POPULATION	

Number	Title1	Title2	Title3
	EMERGENT ADVERSE EVENTS IN THE RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS BODY SYSTEM		
14.3.1.11	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS RELATED TO NEBULIZER	SAFETY POPULATION	
14.3.2.1	OVERALL SUMMARY OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.2.1	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.2.2	TABULATION OF COMMON (>= 5%) TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.3.1	TABULATION OF FATAL TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.3.2	TABULATION OF FATAL TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.2.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.2.5	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL FROM STUDY	SAFETY POPULATION	
14.3.2.6.1	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL OF STUDY TREATMENT	SAFETY POPULATION	
14.3.2.6.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL OF LAI	SAFETY POPULATION	
14.3.2.6.3	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.2.6.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.2.7.1	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING IN INTERRUPTION OF STUDY TREATMENT	SAFETY POPULATION	
14.3.2.7.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING IN INTERRUPTION OF LAI	SAFETY POPULATION	
14.3.2.7.3	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING IN INTERRUPTION OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.2.7.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING IN INTERRUPTION OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.2.8	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS BY MAXIMUM TOXICITY GRADE	SAFETY POPULATION	
14.3.2.9	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS BY RELATIONSHIP TO LAI	SAFETY POPULATION	
14.3.2.10	SUMMARY OF DURATION OF SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.11.1	OVERALL SUMMARY OF HOSPITALIZATIONS DUE TO TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.2.11.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.2.11.3	SUMMARY OF DURATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RESULTING	SAFETY POPULATION	

Number	Title1	Title2	Title3
	IN HOSPITALIZATION		
14.3.2.12	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS RELATED TO NEBULIZER	SAFETY POPULATION	
14.3.3.1.1	OVERALL SUMMARY OF POST-TREATMENT ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.1.2	TABULATION OF POST-TREATMENT ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.2.1	OVERALL SUMMARY OF POST-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.2.2	TABULATION OF POST-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.2.1.1	TABULATION OF FATAL POST-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.2.1.2	TABULATION OF FATAL POST-TREATMENT SERIOUS ADVERSE EVENTS RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.3.3.1	OVERALL SUMMARY OF HOSPITALIZATIONS DUE TO POST-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.3.3.2	TABULATION OF POST-TREATMENT SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.3.3.3	SUMMARY OF DURATION OF POST-TREATMENT SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.4.1.1	OVERALL SUMMARY OF PRE-TREATMENT ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.1.2	TABULATION OF PRE-TREATMENT ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.2.1.1	OVERALL SUMMARY OF PRE-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.2.1.2	TABULATION OF PRE-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.2.2.1	TABULATION OF FATAL PRE-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.2.2.2	TABULATION OF FATAL PRE-TREATMENT SERIOUS ADVERSE EVENTS RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.4.3.1	OVERALL SUMMARY OF HOSPITALIZATIONS DUE TO PRE-TREATMENT SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.4.3.2	TABULATION OF PRE-TREATMENT SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.4.3.3	SUMMARY OF DURATION OF PRE-TREATMENT SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.5.1	OVERALL SUMMARY OF HOSPITALIZATIONS DUE TO SERIOUS ADVERSE EVENTS	SAFETY POPULATION	
14.3.5.2	TABULATION OF SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.5.3	SUMMARY OF DURATION OF SERIOUS ADVERSE EVENTS RESULTING IN HOSPITALIZATION	SAFETY POPULATION	
14.3.6.1	OVERALL SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.6.2	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.6.3	TABULATION OF COMMON (>= 5%) TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	

Number	Title1	Title2	Title3
14.3.6.4	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.6.5	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL FROM STUDY	SAFETY POPULATION	
14.3.6.6.1	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF STUDY TREATMENT	SAFETY POPULATION	
14.3.6.6.2	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF LAI	SAFETY POPULATION	
14.3.6.6.3	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.6.6.4	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.6.7.1	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF STUDY TREATMENT	SAFETY POPULATION	
14.3.6.7.2	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF LAI	SAFETY POPULATION	
14.3.6.7.3	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.6.7.4	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.6.8	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST BY MAXIMUM TOXICITY GRADE	SAFETY POPULATION	
14.3.6.9	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST BY RELATIONSHIP TO LAI	SAFETY POPULATION	
14.3.6.10	SUMMARY OF DURATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST IN THE RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS BODY SYSTEM	SAFETY POPULATION	
14.3.6.11	TABULATION OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST RELATED TO NEBULIZER	SAFETY POPULATION	
14.3.7.1	OVERALL SUMMARY OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.7.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.7.3.1	TABULATION OF FATAL TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.7.3.2	TABULATION OF FATAL TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RELATED TO STUDY TREATMENT	SAFETY POPULATION	
14.3.7.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RELATED TO STUDY TREATMENT	SAFETY POPULATION	

Number	Title1	Title2	Title3
14.3.7.5	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL FROM STUDY	SAFETY POPULATION	
14.3.7.6.1	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF STUDY TREATMENT	SAFETY POPULATION	
14.3.7.6.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF LAI	SAFETY POPULATION	
14.3.7.6.3	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.7.6.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST LEADING TO WITHDRAWAL OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.7.7.1	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF STUDY TREATMENT	SAFETY POPULATION	
14.3.7.7.2	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF LAI	SAFETY POPULATION	
14.3.7.7.3	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.7.7.4	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST RESULTING IN INTERRUPTION OF BOTH LAI AND MULTI-DRUG REGIMEN	SAFETY POPULATION	
14.3.7.8	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST BY MAXIMUM TOXICITY GRADE	SAFETY POPULATION	
14.3.7.9	TABULATION OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST BY RELATIONSHIP TO LAI	SAFETY POPULATION	
14.3.7.10	SUMMARY OF DURATION OF SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST	SAFETY POPULATION	
14.3.8.1	SUMMARY OF TREATMENT-EMERGENT COUGH CHARACTERISTICS	SAFETY POPULATION	
14.3.8.2	SUMMARY OF TREATMENT-EMERGENT SERIOUS COUGH CHARACTERISTICS	SAFETY POPULATION	
14.3.9.1.1	SUMMARY OF CLINICAL LABORATORY RESULTS	CHEMISTRY	SAFETY POPULATION
14.3.9.2.1	SUMMARY OF CLINICAL LABORATORY RESULTS	HEMATOLOGY	SAFETY POPULATION
14.3.9.1.2	SHIFT TABLE OF CLINICAL LABORATORY RESULTS	CHEMISTRY	SAFETY POPULATION
14.3.9.2.2	SHIFT TABLE OF CLINICAL LABORATORY RESULTS	HEMATOLOGY	SAFETY POPULATION
14.3.10	SUMMARY OF VITAL SIGNS	SAFETY POPULATION	
14.3.11.1	SUMMARY OF AUDIOLOGY TESTS (DECIBELS)	SAFETY POPULATION	
14.3.11.2	TABULATION OF AUDIOLOGY HEARING LOSS BY VISIT	SAFETY POPULATION	
14.3.11.3	SHIFT TABLE OF AUDIOLOGY HEARING LOSS BY VISIT	SAFETY POPULATION	

Number	Title1	Title2	Title3
14.3.13	TABULATION OF ELECTROCARDIOGRAM RESULTS	SAFETY POPULATION	

Figures

Number	Title1	Title2	Title3
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14.2.3.2	PLOT OF MEAN CHANGE-FROM-BASELINE IN 6-MINUTE WALK TEST DISTANCE (M) BY VISIT	OBSERVED DATA	SAFETY POPULATION
14.2.6.1	PLOT OF MEAN BODY MASS INDEX (KG/M2) BY VISIT	SAFETY POPULATION	
14.2.6.2	PLOT OF MEAN CHANGE-FROM-BASELINE IN BODY MASS INDEX (KG/M2) BY VISIT	SAFETY POPULATION	
14.3.11.1.1	PLOT OF MEAN AUDIOLOGY TESTS (DECIBELS)	SAFETY POPULATION	
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16.2.4	END OF TREATMENT	ENROLLED SUBJECTS	
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16.2.6	INCLUSION/EXCLUSION CRITERIA FAILURES	ALL SUBJECTS	
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16.2.9.1	DEMOGRAPHICS	ALL SUBJECTS	
16.2.9.2	DEMOGRAPHICS – IF FEMALE,	ALL FEMALE SUBJECTS	
16.2.10	MEDICAL HISTORY	ALL SUBJECTS	
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16.2.16.1	SPUTUM SAMPLE CRF	ALL SUBJECTS	
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Number	Title1	Title2	Title3
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16.2.20	ST. GEORGE'S RESPIRATORY QUESTIONNAIRE	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.21	EUROQOL 5D (EQ-5D-3L)	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.22.1	6-MINUTE WALK TEST – PART 1	DISTANCE WALKED	ALL SUBJECTS
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16.2.23.1	ADVERSE EVENTS	ALL SUBJECTS	ALL SUBJECTS
16.2.23.2	SERIOUS ADVERSE EVENTS	ALL SUBJECTS	ALL SUBJECTS
16.2.23.3	FATAL ADVERSE EVENTS	ALL SUBJECTS	ALL SUBJECTS
16.2.23.4	ADVERSE EVENTS RESULTING IN HOSPITALIZATION	ALL SUBJECTS	ALL SUBJECTS
16.2.23.6	COUGH ADVERSE EVENTS	ALL SUBJECTS	ALL SUBJECTS
16.2.23.7	ADVERSE EVENTS OF SPECIAL INTEREST	ALL SUBJECTS	ALL SUBJECTS
16.2.23.8	SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST	ALL SUBJECTS	ALL SUBJECTS
16.2.24	MEDICATIONS	ALL SUBJECTS	ALL SUBJECTS
16.2.26.1	HEALTH CARE RESOURCE UTILIZATION – HOSPITALIZATIONS	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.26.2	HEALTH CARE RESOURCE UTILIZATION – HOSPITALIZATIONS – ICU ADMISSIONS	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.26.3	HEALTH CARE RESOURCE UTILIZATION – EMERGENCY ROOM VISITS	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.26.4	HEALTH CARE RESOURCE UTILIZATION – DOCTOR VISITS	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.26.5	HEALTH CARE RESOURCE UTILIZATION – OTHER	ENROLLED SUBJECTS	ALL

Number	Title1	Title2	Title3
			SUBJECTS
16.2.27.1	LAI ADMINISTRATION – ON-SITE ADMINISTRATION	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.27.2	LAI ADMINISTRATION – SUBJECT DOSING	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.27.3	LAI DRUG ACCOUNTABILITY	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.27.4	LAI MISSED DOSES	ENROLLED SUBJECTS	ALL SUBJECTS
16.2.27.5	LAI COMPLIANCE	ENROLLED SUBJECTS	ALL SUBJECTS

11.2. Data Display Specifications

File formats

Unless otherwise specified, all outputs should be in RTF file format.

Page format

For submissions in the US, all outputs are presented in landscape orientation on 8.5x11 inch paper with Times New Roman or Courier New type face, 9-point font unless otherwise specified, and 1-inch margins on all sides.

For submissions in the EU, all outputs are presented in landscape orientation on A4 paper with Times New Roman or Courier New type face, 9-point font unless otherwise specified, and 2cm margins on all sides.

The hyphen (-) in table titles in the mock-ups indicates a line break.

Regions

Regions are, in order of appearance, 'All', 'North America', 'Japan', 'Europe', 'Oceania', and 'Asia (excluding Japan)'. When presenting data by region, there should be an 'All' group for each country and then the sites within that country should appear following the country. For categorical data, all categories should appear within each site.

Within each region the countries will be ordered by descending number of subjects enrolled to sites within that country. Similarly, within country the sites will be ordered by descending number of subjects enrolled to the sites.

On all tables by region, country, and site put a page break after each site.

Percentages

Unless otherwise indicated, percentages presented on a table will be based on the number of subjects in the column. Exceptions to this rule will be indicated in the footnote of those tables. If the count in a table is zero (0), only the count (0) should appear in the cell on the table (ie, no percentages or, in the case of AE tables, event counts). If there is a 100% there should be no decimal places presented (ie, 100% is 100).

Change-from-baseline Summaries

Tables of continuously valued parameters presenting change-from-baseline summaries will present, within each visit, 3 blocks of summary statistics for the observed cases (ie available data). The first block will present the 'actual', the second block will present, 'baseline' and the third block will present the 'change-from-baseline'. The 'actual' block will summarize the value collected at that visit. The 'baseline' block will summarize the baseline value for those subjects who have non-missing 'actual' values at the visit. The 'change-from-baseline' block will summarize the change-from-baseline value for subjects with non-missing 'actual' and 'baseline' values at the visit.

Mock-ups

Mock-ups of tables and listings are provided in separate documents.

11.3. Schedule of Events

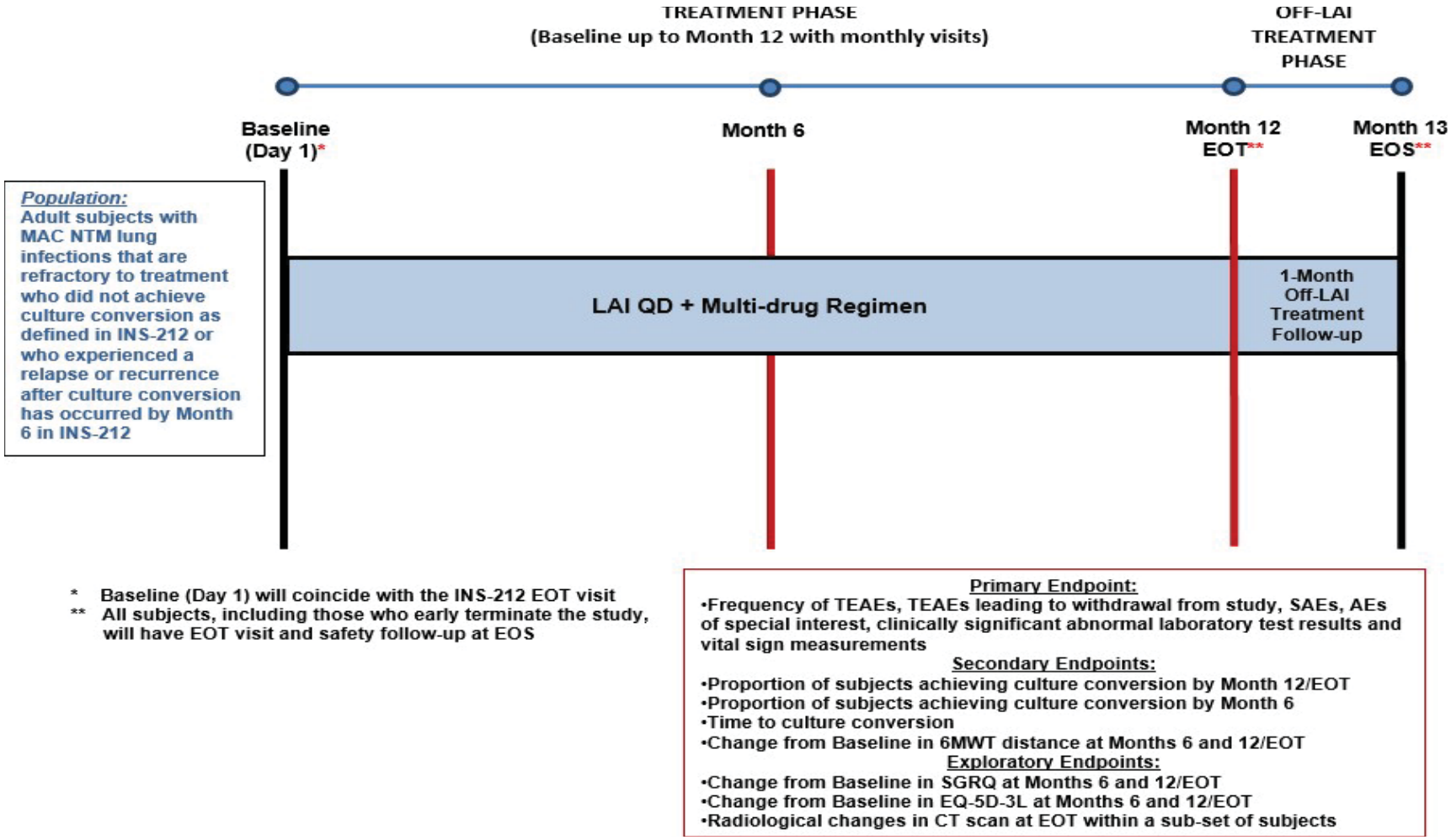
INS-312	TREATMENT PHASE													OFF-ALIS TREATMENT PHASE
	Baseline	Month 1	Month 2[a]	Month 3	Month 4 [a]	Month 5 [a]	Month 6	Month 7 [a]	Month 8 [a]	Month 9	Month 10 [a]	Month 11 [a]	EOT Month 12	EOS up to Month 13
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)
Visit Window	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Informed Consent[b]	X	–	–	–	–	–	–	–	–	–	–	–	–	–
Medical History[c]	X	–	–	–	–	–	–	–	–	–	–	–	–	–
Pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	–
SGRQ (Part I and II)	X	–	–	–	–	–	X	–	–	–	–	–	X	X
EQ-5D-3L	X	–	–	–	–	–	X	–	–	–	–	–	X	X
Physical examination	X	X	–	X	–	–	X	–	–	X	–	–	X	X
Body weight	X	X	–	X	–	–	X	–	–	X	–	–	X	X
Vital signs and pulse oximetry[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6 minute walk test	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Audiology test	X[f]	–	–	–	–	–	X	–	–	–	–	–	X	–
Concomitant medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare Resource Utilization	X	X	–	X	–	–	X	–	–	X	–	–	X	–
AE assessment[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum collection for microbiology	X	X	X	X	X	X	X	X	X	X	X	X	X	–

INS-312	TREATMENT PHASE													OFF-ALIS TREATMENT PHASE
	Baseline	Month 1	Month 2[a]	Month 3	Month 4 [a]	Month 5 [a]	Month 6	Month 7 [a]	Month 8 [a]	Month 9	Month 10 [a]	Month 11 [a]	EOT Month 12	EOS up to Month 13
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)
Visit Window	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Chemistry	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Hematology	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Urinalysis	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Serum for biomarkers (CRP and IL-6)	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Sub-Study: CT scan of chest[i]	X	–	–	–	–	–	–	–	–	–	–	–	X	–
Sub-Study: CT scan of chest[j] (Japan)	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Send sputum collection containers home	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Administer study drug at site	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Dispense study drug[k]	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Collection of study drug vials	–	X	X	X	X	X	X	X	X	X	X	X	X	–

[a] Home Healthcare visits may be available for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits.
[b] Subjects will be asked to provide written informed consent at their INS-212 EOT visit.
[c] All ongoing medical history conditions from INS-212 must be listed within the medical history eCRF for INS-312. Any chronic conditions that require medication must be listed in the medical history eCRF.
[d] Urine pregnancy testing will be performed on all women of child bearing potential. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
[e] At visits where study drug is administered, vital signs and pulse oximetry will be performed before and after study drug administration.
[f] The Baseline audiology examination must be performed on Day 1 before the administration of study drug.
[g] All ongoing medication(s) from the INS-212 study must be documented in the concomitant medication eCRF for INS-312; this includes any ongoing medication(s) that were recorded in INS-212 prior to the first dosing in INS-312.

[h] All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. At visits where study drug is administered, AEs will be assessed before and after administration of study drug. Any AE that has occurred and resolved before administration of the study drug on Day 1 (Baseline) will be documented for studyINS-212.
[i] Only for subjects who agreed to participate in the CT Scan sub-study in INS-312. Subjects will have a chest CT scan at Baseline (Day 1), if not already done at the INS-212 EOT Visit. Subjects will have a follow-up chest CT scan at the EOT visit, provided the last chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available. Please refer to APPENDIX 3 for additional details on the CT Scan sub-study.
[j] Only for subjects in Japan. Subjects will have a chest CT scan at Baseline (Day 1), if not already done at the INS-212 Month 6 visit. Subjects will also have chest CT scans at Month 6 and at the EOT visit, provided the last chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available. Please refer to APPENDIX 4 for additional details on the Japan specific CT Scan sub-study.
[k] Study drug will be dispensed to all subjects up to and including the Month 11 visit.

11.4. INS-312 Study Schematic



Statistical Analysis Plan

Insmed Incorporated

Protocol: INS-312

An Open-Label Safety Extension Study to a 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

Protocol Version: 3.1

Protocol Date: 25 May 2017

Sponsor: Insmed Incorporated
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Version	Date
Final	06 June 2017

Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

Signature	Date
[redacted]	06-JUN-2017
[redacted] Insmed Inc.	08 JUNE 2017

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LIST OF ABBREVIATIONS

The following abbreviations are used in this document.

Table 1: List of Abbreviations and Definitions

Abbreviation	Term
6MWT	Six-minute walk test
6MWD	6-minute walk distance
AE	Adverse event
ATC	Anatomical/Therapeutic/Chemical
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DMC	Data monitoring committee
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EQ-5D-3L	Formerly EuroQol 5D, a generic health-status classification instrument
ICH	International conference on harmonisation
LAI	Liposomal amikacin for inhalation
MAC	Mycobacterium avium complex
MedDRA	Medical dictionary for regulatory activities
NTM	Nontuberculous mycobacteria
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WHO	World Health Organization

DEFINITIONS

Safety Population	The safety population is the set of all enrolled subjects who received at least 1 dose of Liposomal amikacin for inhalation (LAI).

Adverse Event	Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Treatment-emergent Adverse Event	Treatment-emergent adverse events (TEAEs) are Adverse event (AEs) that occurred on or after the date of first dose of study medication in study INS-312 and within 1 month (28 days) after the last dose in study INS-312.

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented for the analyses of data collected within the scope of Insmed Incorporated Protocol INS-312 [An Open-Label Safety Extension Study to a 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] for accelerated submission. This SAP was developed by Insmed.

This SAP is based on:

- Protocol INS-312, version # 1.0, dated 10 September 2015
- Protocol INS-312, amendment 2, dated 13 July 2016
- Protocol INS-312, amendment 3, dated 16 May 2017
- Protocol INS_312, amendment 3.1, dated 25 May 2017
- International Conference on Harmonization (ICH) guidance E9 (Statistical Principles for Clinical Trials)

All decisions regarding analyses, including SAP finalization, will be approved prior to database lock. Deviations from the approved plan will be noted in the clinical study report (CSR).

The study will be split into two sets of analyses. The first analysis will support accelerated regulatory submission, and the second will be done at study completion. The accelerated submission will be based on all available safety data at the data cutoff date. Available efficacy data up to Month 6 of the study will be used. Any efficacy data available beyond Month 6 will not be included in the accelerated submission.

2. STUDY OBJECTIVES

2.1 End of Study Objectives

2.1.1 Primary Objective (Safety)

The primary objective is to evaluate long term safety and tolerability of LAI (590 mg) administered once daily (QD) for up to 12 months in subjects who were refractory to standard multi-drug treatment and failed to convert in Study INS-212.

2.1.2 Secondary Objectives (Efficacy)

1. To evaluate the number of subjects achieving culture conversion (3 consecutive negative sputum cultures) by Month 12/EOT (end of treatment)
2. To evaluate the number of subjects achieving culture conversion by Month 6
3. To evaluate the time to culture conversion
4. To evaluate the change in the six-minute walk test (6MWT) distance at Month 6 and Month 12/EOT

2.1.3 Exploratory Objectives (Efficacy)

1. To assess subject-reported symptoms of NTM and change from Baseline in quality of life scores on the St George's Respiratory Questionnaire (SGRQ) and quality of life scores on the SGRQ – Part 2 (Activities of Daily Living) at Month 6 and Month 12/EOT
2. To assess the change from Baseline in the EQ-5D-3L questionnaire subject-reported health outcomes at Month 6 and Month 12/EOT

2.2 Objectives for Accelerated Submission

2.2.1 Primary Objective (Safety)

The primary objective is to evaluate long term safety and tolerability of LAI (590 mg) administered once daily (QD) for up to 12 months in subjects who were refractory to standard multi-drug treatment and failed to convert in Study INS-212.

2.2.2 Secondary Objectives (Efficacy)

1. To evaluate the number of subjects achieving culture conversion (3 consecutive negative sputum cultures) by Month 6
2. To evaluate the time to culture conversion
3. To evaluate the change in the six-minute walk test (6MWT) distance at Month 6

2.2.3 Exploratory Objectives (Efficacy)

1. To assess subject-reported symptoms of NTM and change from Baseline in quality of life scores on the St George's Respiratory Questionnaire (SGRQ) and quality of life scores on the SGRQ – Part 2 (Activities of Daily Living) at Month 6
2. To assess the change from Baseline in the EQ-5D-3L questionnaire subject-reported health outcomes at Month 6

3. STUDY DESIGN AND PLAN

Eligible subjects will have successfully completed their Month 6 visit in the INS-212 study. At or after all the INS-212 Month 6 visit assessments have been completed, the investigator will remind the subject of the potential opportunity to enroll in INS-312 at their scheduled Month 8 visit, to allow sufficient time for the subject to make an informed decision. At the scheduled Month 8 visit, eligible subjects will be confirmed to have not achieved the INS-212 protocol definition of culture conversion (3 consecutive negative sputum cultures) or to have experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred), as determined by the subjects' Day 1 through Month 6 sputum assessments in INS-212. The scheduled Month 8 visit will become the EOT visit. Subjects will be asked to provide written informed consent and will enroll directly from the INS-212 study at their EOT visit when all sputum results from Day 1 through Month 6 are known, and after having met all eligibility criteria.

All enrolled subjects will receive LAI administered QD added to a multi-drug regimen for 12 months. All subjects will return 1 month after EOT for an off-LAI treatment follow-up visit at the end of study (EOS) visit.

The EOT study visit for the INS-212 study will be Day 1 for the INS-312 study. Expectorated sputum (spontaneous or induced eg, with nebulized hypertonic saline solution as needed) collected at the INS-212 EOT study visit will be used as the Baseline sputum for the INS-312 study. All subjects will have at least 2 sputum specimens collected by every scheduled visit during the treatment phase. Subjects must interrupt LAI administration for 2 days prior to all schedule study visits. If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable.

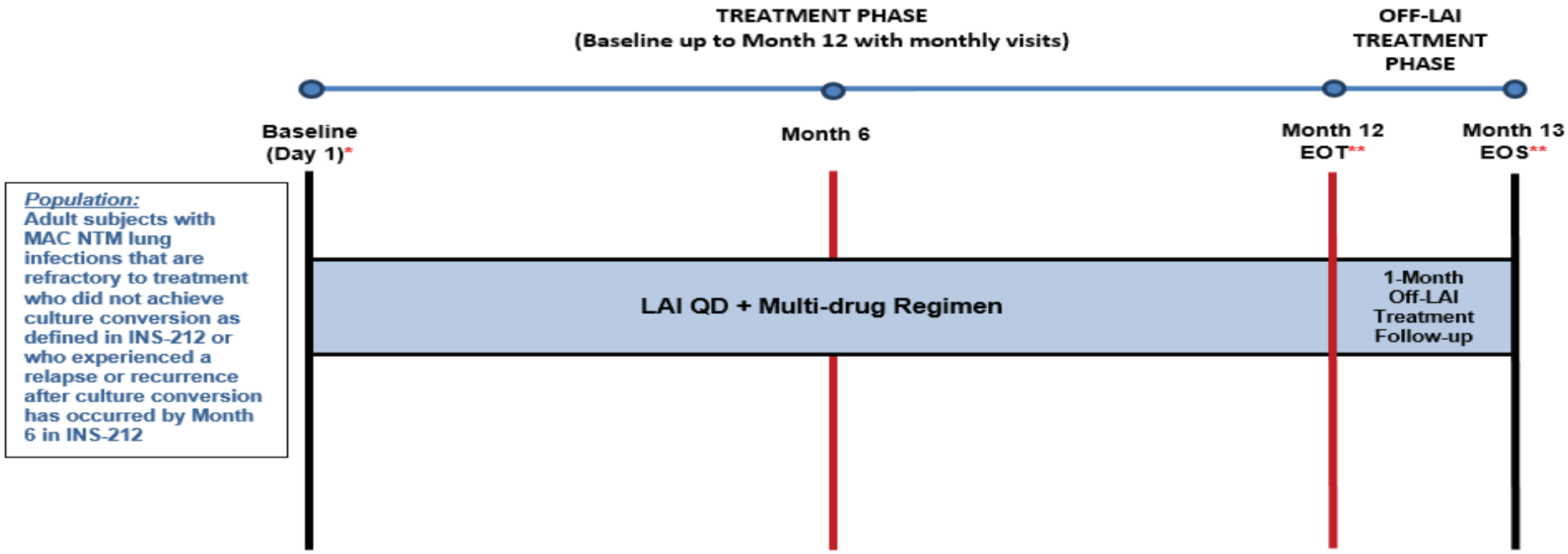
All subjects will have monthly routine visits at Day 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12/EOT. At these visits a physical examination (including vital signs, pulse oximetry and weight) will be performed. Safety lab assessments (chemistry, hematology, and urinalysis), a pregnancy test (if woman of child bearing potential), and a healthcare utilization questionnaire will be conducted at Day 1, Months 1, 3, 6, 9, and 12/EOT. The

6MWT, audiology test, SGRQ, and EQ-5D-3L will be assessed at Day 1 and Months 6 and 12/EOT. Any procedure performed at EOT in the INS-212 study will be used as the Baseline measurement for the INS-312 study and will not need to be performed a second time.

All subjects will return 1 month after EOT for an off-LAI treatment follow-up visit (EOS); this includes subjects that discontinued study drug early as both the EOT and EOS visits will need to occur. At this visit, a physical examination (including vital signs, pulse oximetry and weight), SGRQ, and EQ-5D-3L will be performed. Unscheduled visits will occur as needed should subjects' symptoms worsen between visits.

Figure 1: Study Design

Figure 1 shows a schematic of the study design.



* Baseline (Day 1) will coincide with the INS-212 EOT visit
** All subjects, including those who early terminate the study, will have EOT visit and safety follow-up at EOS

Primary Endpoint:
- Frequency of TEAEs, TEAEs leading to withdrawal from study, SAEs, AEs of special interest, clinically significant abnormal laboratory test results and vital sign measurements

Secondary Endpoints:
- Proportion of subjects achieving culture conversion by Month 12/EOT
- Proportion of subjects achieving culture conversion by Month 6
- Time to culture conversion
- Change from Baseline in 6MWT distance at Months 6 and 12/EOT

Exploratory Endpoints:
- Change from Baseline in SGRQ at Months 6 and 12/EOT
- Change from Baseline in EQ-5D-3L at Months 6 and 12/EOT
- Radiological changes in CT scan at EOT within a sub-set of subjects

4. SCHEDULE OF EVENTS

Table 2 shows the schedule of assessments.

Table 2: Schedule of Events

INS-312	TREATMENT PHASE													OFF-LAI TREATMENT PHASE
	Baseline	Month 1	Month 2[a]	Month 3	Month 4[a]	Month 5[a]	Month 6	Month 7[a]	Month 8[a]	Month 9	Month 10[a]	Month 11[a]	EOT Month 12	EOS up to Month 13
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)
Visit Window	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Informed Consent[b]	X	–	–	–	–	–	–	–	–	–	–	–	–	–
Medical History[c]	X	–	–	–	–	–	–	–	–	–	–	–	–	–
Pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	–
SGRQ (Part I and II)	X	–	–	–	–	–	X	–	–	–	–	–	X	X
EQ-5D-3L	X	–	–	–	–	–	X	–	–	–	–	–	X	X
Physical examination	X	X	–	X	–	–	X	–	–	X	–	–	X	X
Body weight	X	X	–	X	–	–	X	–	–	X	–	–	X	X
Vital signs and pulse oximetry[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6 minute walk test	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Audiology test	X[f]	–	–	–	–	–	X	–	–	–	–	–	X	–
Concomitant medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare Resource Utilization	X	X	–	X	–	–	X	–	–	X	–	–	X	–

INS-312	TREATMENT PHASE													OFF-LAI TREATMENT PHASE
	Baseline	Month 1	Month 2[a]	Month 3	Month 4[a]	Month 5[a]	Month 6	Month 7[a]	Month 8[a]	Month 9	Month 10[a]	Month 11[a]	EOT Month 12	EOS up to Month 13
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)
Visit Window	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
AE assessment[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum collection for microbiology	X	X	X	X	X	X	X	X	X	X	X	X	X	–
Chemistry	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Hematology	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Urinalysis	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Serum for biomarkers (CRP and IL-6)	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Sub-Study: CT scan of chest[i]	X	–	–	–	–	–	–	–	–	–	–	–	X	–
Sub-Study: CT scan of chest[j] (Japan)	X	–	–	–	–	–	X	–	–	–	–	–	X	–
Send sputum collection containers home	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Administer study drug at site	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Dispense study drug[k]	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Collection of study drug vials	–	X	X	X	X	X	X	X	X	X	X	X	X	–

Note: At visits where study drug is administered, all subject-reported outcomes, 6MWT, and physical exam should be performed pre-dose**.**
Any procedure performed at EOT in the INS-212 study will be used as the Baseline (Day 1) measurement for this study and will not need to be performed a second time. It is possible and acceptable that procedures in INS-212 will be performed prior to the INS-312 informed consent being signed.
Abbreviations: AE, Adverse Event; CT, computed tomography; EOS, End of Study; EOT, End of Treatment; EQ-5D-3L, EuroQol 5D; SGRQ, St. George's Respiratory Questionnaire.
[a] Home Healthcare visits may be available for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits.

[b] Subjects will be asked to provide written informed consent at their INS-212 EOT visit.
[c] All ongoing medical history conditions from INS-212 must be listed within the medical history eCRF for INS-312. Any chronic conditions that require medication must be listed in the medical history eCRF.
[d] Urine pregnancy testing will be performed on all women of child bearing potential. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
[e] At visits where study drug is administered, vital signs and pulse oximetry will be performed before and after study drug administration.
[f] The Baseline audiology examination must be performed on Day 1 before the administration of study drug.
[g] All ongoing medication(s) from the INS-212 study must be documented in the concomitant medication eCRF for INS-312; this includes any ongoing medication(s) that were recorded in INS-212 prior to the first dosing in INS-312.
[h] All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. At visits where study drug is administered, AEs will be assessed before and after administration of study drug. Any AE that has occurred and resolved before administration of the study drug on Day 1 (Baseline) will be documented for study INS-212.
[i] Only for subjects who agreed to participate in the CT Scan sub-study in INS-312. Subjects will have a chest CT scan at Baseline (Day 1), if not already done at the INS-212 EOT Visit. Subjects will have a follow-up chest CT scan at the EOT visit, provided the last chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available. Please refer to APPENDIX 3 for additional details on the CT Scan sub-study.
[j] Only for subjects in Japan. Subjects will have a chest CT scan at Baseline (Day 1), if not already done at the INS-212 Month 6 visit. Subjects will also have chest CT scans at Month 6 and at the EOT visit, provided the last chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available. Please refer to APPENDIX 4 for additional details on the Japan specific CT Scan sub-study.
[k] Study drug will be dispensed to all subjects up to and including the Month 11 visit.

INS-312	TREATMENT PHASE													OFF LAI TREATMENT PHASE
	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	EOT Month 12	EOS up to Month 13
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)
Visit Window[a]	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Chemistry	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Hematology	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Urinalysis	X	X	–	X	–	–	X	–	–	X	–	–	X	–
Send sputum collection containers home	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Administer study drug at site	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Dispense study drug[j]	X	X	X	X	X	X	X	X	X	X	X	X	–	–
Collection of study drug vials	–	X	X	X	X	X	X	X	X	X	X	X	X	–

Note: At visits where study drug is administered, all subject-reported outcomes, 6MWT, and physical exam should be performed pre-dose.
Any procedure performed at EOT in the INS-212 study will be used as the Baseline (Day 1) measurement for this study and will not need to be performed a second time.
Abbreviations: AE, Adverse Event; EOS, End of Study; EOT, End of Treatment; SGRQ, St. George's Respiratory Questionnaire.

[a] Visit window for all visits is ±3 days.
[b] Subjects will be asked to provide written informed consent at their INS-212 EOT visit.
[c] All ongoing medical history conditions from the INS-212 must be listed within the medical history eCRF for INS-312. Any chronic conditions that require medication must be listed in the medical history eCRF.
[d] Urine pregnancy testing will be performed on all women of child bearing potential. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
[e] Subject-reported outcomes will be obtained before study drug administration.
[f] At visits where study drug is administered, vital signs and pulse oximetry will be performed before study drug administration and reassessed after study drug administration.
[g] The Baseline audiology examination must be performed on Day 1 before the administration of study drug.
[h] All ongoing medication(s) from the INS-212 study must be documented in the concomitant medication eCRF for INS-312; this includes any ongoing medication(s) that were recorded in INS-212 prior to the first dosing in INS-312.

[i] All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. At visits where study drug is administered, AEs will be assessed before and after administration of study drug. Any AE that has occurred before administration of the study drug on Day 1 (Baseline) and was resolved will be documented for study INS-212.
[k] All subjects will have at least 2 expectorated sputum collected by every scheduled visit during the treatment phase. Subjects must interrupt LAI administration for approximately 72 hours prior to all schedule study visits. If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable. LAI dosing will resume once the sputum sample has been obtained at the site.
[l] Study drug will be dispensed to all subjects up to and including the Month 11 visit.

5. DISCUSSION OF STUDY DESIGN

5.1 Number of Subjects

It is expected that approximately 200 subjects will be eligible for and enroll in this study.

5.2 Study Duration

Subjects will remain in the study for up to 13 months, up to 12 months in the open label treatment phase plus 1 month in the off-LAI treatment phase. Each subject will receive LAI treatment in the study for up to 12 months. Subjects will enroll directly from the INS-212 study at their EOT visit when all sputum results from Day 1 through Month 6 are known.

The study will be split into two sets of analyses. The first analysis will support accelerated regulatory submission, and the second will be done at study completion. The accelerated submission will be based on all available safety data at the data cutoff date. Available efficacy data up to Month 6 of the study will be used. Any efficacy data available beyond Month 6 will not be included in the accelerated submission.

5.3 Assignment to Study Drug

All eligible subjects will receive the same treatment (LAI 590 mg QD) in addition to the multi drug regimen.

5.4 Data Monitoring Committee

To ensure the safety of subjects enrolled in INS-312, Insmed plans to implement a Data Monitoring Committee (DMC). The Committee will consist of experts outside of Insmed who are not involved in the study conduct. The DMC will provide a centralized review function independent of Insmed clinical team and all other individuals associated with the conduct of the study. The DMC will be comprised of at least two physicians with pulmonary expertise who are not investigators in the clinical study and a statistician who is experienced in the evaluation of safety data. Further details are provided in the DMC charter.

6. DETERMINATION OF SAMPLE SIZE, STRATIFCATION AND METHOD OF RANDOMIZATION

6.1 Sample Size

There is no formal sample size determination as this study follows the INS-212 study and all eligible subjects who consent after Month 6 and complete the EOT visit of the INS-212 study may enroll in this study.

6.2 Stratification

Not applicable.

6.3 Randomization and Blinding

Not applicable.

7. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures, with subjects classified per their assigned INS-212 treatment. The ICH numbering convention will be used for all outputs. Unless otherwise noted, all statistical testing (if any) will be two-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated p-value is < 0.05.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All data that meaningfully contribute to the objectives of the study will be included. Footnotes will specify the basis for the percentages. For percentages of subjects, the denominator will generally be the number of subjects in the analysis set and INS-212 treatment arm. All summary tables will be presented by INS-212 treatment arm. A total summary column may be included in some summary tables where relevant.

Summaries of continuous variables that have some values recorded using approximate values (eg, < or >) will use the numeric part of the value in calculations. Listings will present the data in its original format.

For summaries where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place ie, integers), values $\geq$ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

Individual subject data obtained from the electronic case report forms (eCRFs), and any derived data will be presented by site, INS-212 treatment arm and subject in data listings.

Post-baseline unscheduled visit data will be presented in the listings only (ie, unscheduled visit data will not be summarized in tables). If a subject has more than one observation at a visit for any reason, the average of the observations will be used in summary tables.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any other analyses performed will be considered post-hoc. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® version 9.4 or higher. Tables, listings, and figures will be presented in rich text format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation and senior review process will be used to confirm that all data manipulations and calculations and statistical analysis results are accurate and that statistically-valid methods have been implemented. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

8. ANALYSIS POPULATIONS

8.1 Safety Population

The safety population is the set of all enrolled subjects who received at least 1 dose of LAI under the INS-312 protocol.

9. STUDY POPULATION

9.1 Subject Disposition

Subject disposition information will be summarized for all subjects by INS-212 treatment arm and overall. Summaries will include: the number of enrolled subjects, the number of subjects in safety population, the number of subjects completing the study, and the primary reason for discontinuation.

9.2 Protocol Deviations

Protocol deviations that could potentially affect the safety conclusion of the study will be identified prior to database lock.

A listing of all protocol deviations including the deviation designation (major or minor) and category will be presented in a data listing.

Major protocol deviations will be summarized by deviation category (ie, compliance, prohibited medication, etc.) and INS-212 treatment arm.

9.3 Demographic and Baseline Characteristics

Demographic variables include: country, age, sex, ethnicity and race. Age will be calculated in years relative to the informed consent date in INS-212. Demographic variables will be summarized by geographic region and overall. Descriptive statistics will be presented for age. Frequency counts and percentages will be presented for region, country, sex, ethnicity, race and stratification criteria.

Eligibility criteria (inclusion/exclusion) not met by subjects who screen failed will be presented in a listing.

Enrolled subjects who are eligible but excluded from the safety population will also be listed.

9.4 Medical History and Medical Conditions Present at Entry

Ongoing Medical History and/or adverse events that are continuing from INS-212 will be collected in Medical History eCRF page. All adverse events (AEs) that occur between the time a subject signs the informed consent for INS-312 and receives his/her first dose in INS-312 will be considered as medical history and not as an AE unless the event worsens in severity after treatment start. The general medical history will be summarized by System Organ Class and preferred term.

9.5 Concomitant Medications

Concomitant medications are those medications taken on or after the first dose (Day 1) of study drug in INS-312. All ongoing medication(s) that were recorded in INS-212 prior to the first dosing in INS-312 will be considered as concomitant medications in INS-312.

Concomitant medications will be summarized for each INS-212 treatment arm by World Health Organization (WHO) Drug Dictionary (WHODDE B2 format, September 2016) Anatomical/Therapeutic/Chemical (ATC) classes ATC1 (Anatomic) and ATC2 (Therapeutic). These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC class and preferred

name. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class. The tables for medications will be sorted by decreasing frequency of ATC1 followed by ATC2 based on the total incidence across treatment arms. In case of equal frequency regarding ATC1 (respectively ATC2), alphabetical order will be used. Prior medications will be summarized for overall subjects by WHO ATC classes ATC1 (Anatomic) and ATC2 (Therapeutic) similarly to concomitant medications.

10. SECONDARY AND EXPLORATORY EFFICACY ANALYSES

All efficacy analyses will be based on the safety population.

10.1 Efficacy Endpoints

Sputum Culture Conversion:

Each subject in the safety population is classified as either a converter or non-converter. The efficacy endpoint is the proportion of subjects achieving culture conversion by Month 12/EOT (end of treatment)

Sputum specimens are collected at screening, baseline (Day 1), and at Months 1 through 12. Culture conversion by Month 6 is defined as 3 consecutive monthly negative sputum cultures by Month 6 (inclusive). For example, a Month 4 culture conversion will have negative sputum cultures at Months, 4, 5 and 6. All other subjects will be (Month 6) non-converters. Subjects with missing sputum culture results for which culture conversion cannot be evaluated will be considered as non-converters.

For accelerated submission, the efficacy analysis of culture conversion by Month 6 will be based on all subjects with at least 6 months of culture conversion data.

Time to culture conversion:

The date of conversion for subjects achieving culture conversion is defined as the date of the first of 3-consecutive monthly negative sputum cultures. Then, the number of days to culture conversion is defined as the difference between the date of conversion and the date of first dose of LAI

$$Culture\ Conversion_{days} = Date\ of\ Conversion - Date\ of\ First\ Dose\ of\ LAI + 1$$

This duration in days will then be converted to months using the formula

$$Culture\ Conversion_{months} = \left(\frac{12}{365.25}\right) \cdot Culture\ Conversion_{days}$$

For subjects not achieving culture conversion by Month 6, time to (Month 6) culture conversion is censored at the subject's last day on the study or on the day of their Month 4 visit (whichever is earlier).

Six-minute walk test :

The 6MWD is the distance walked in 6 minutes. The endpoint is the change from baseline to all study visits in actual 6MWD.

St. George's Respiratory Questionnaire

The endpoint is the change from baseline to all study visits in the total score. The SGRQ responses are used to assess the subjects' quality of life by evaluating 3 health domains: symptoms (Part 1), and activity and impacts (both Part 2). Higher domain scores indicate more limitations. The composite total score is derived from the 3 domain scores. Each domain score and the total score has a range of 0 to 100, with 0 indicating the best possible quality of life.

EQ-5D-3L:

The change from baseline (Day 1) in the EQ-5D-3L subject reported health outcomes to all study visits. The EQ-5D-3L consists of two parts. One is a descriptive system of questions and the other an EQ visual analogue scale (EQ-5D-VAS) measurement. The EQ-5D-3L descriptive system is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension the response has 3 levels: no problems, some problems, extreme problems. A single index score will be calculated from the response for the 5 dimensions. The index score will be calculated using United Kingdom weights. The algorithm for index value derivation is provided by the EuroQol Group Foundation [1]. The EQ-5D-3L index scores ranges from 0 to 1; 0 meaning death and 1 complete health. The EQ-5D-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information will be used as a quantitative measure of health outcome as judged by the subjects.

CT Scan (substudy)

For subjects participating in the CT scan sub-study, CT scan results will be qualified as 'normal', 'abnormal – not clinically significant' or 'abnormal – clinically significant' at baseline and 'improved', 'worsened' or 'no change from previous' at post-baseline assessments. The number and percent of subjects within each CT scan category will be summarized by scheduled visits.

Subject reported symptoms of Nontuberculous Mycobacteria:

The incidence of subjects who reported symptoms of NTM lung infections caused by MAC that are refractory to treatment will be summarized by scheduled visits.

10.2 Baseline Values

Last non-missing value on or before the first dose of study medication in INS-312 study will be used as the Baseline. An unscheduled visit may be used in the determination of baseline values, if it provides the last non-missing value prior to the first dose of the study drug in study INS-312.

10.3 Adjustments for Covariates

No adjustments for covariates are planned.

10.4 Handling of Dropouts or Missing Data

The handling of missing sputum culture results is built into the determination of whether a subject achieves culture conversion. For each culture conversion endpoint, all subjects are classified as either a converter or a non-converter. Refer to Section 10.1 for details.

For all other endpoints, missing data will not be imputed and will be considered as missing in statistical analyses.

10.5 Examination of Subgroups

No subgroup analyses are planned.

10.6 Adjustments for Multiple Testing

No adjustments for multiple testing are planned.

10.7 Multicenter Studies

The study will enroll subjects at approximately 150 sites in North America, Europe, and Asia-Pacific regions. Thus, the number of subjects per site will be small. No investigation of site effect is planned and site will not be included as a factor in any analyses.

11. METHODS OF EFFICACY ANALYSIS

Unless otherwise stated, the safety population will be used for all efficacy analyses.
For all efficacy data (Sputum Culture Conversion, 6MWD, SGRQ, EQ-5D-3L and Subject reported symptoms of NTM) observed values and changes from Baseline for continuous variables, absolute and relative frequencies for categorical observations, and shift tables from Baseline to last observation will be summarized overall and by the treatment group in INS-212 using descriptive statistics.

Time to Culture Conversion:
Time to culture conversion is defined in Section 10.1.

Kaplan-Meier curves of the percentage of subjects achieving conversion will be determined for each of the two INS-212 treatment arms and presented in a figure. Also, the median time to conversion together with the 25^{th} and 75^{th} percentiles and their associated 95% Confidence intervals (CIs) will be presented for the two INS-212 treatment arms.

The following lines provide sample SAS code for the Kaplan-Meier curves and estimates.

```
PROC LIFETEST DATA = INPUT_DATA METHOD = KM;
    TIME MONTHS * CENSOR (1);
    STRATA TRT;
```

MONTHS is the number of months, rounded to the nearest integer, to culture conversion (based on either the date of conversion or the date of censoring). TRT is the treatment and CENSOR is an indicator variable that indicates whether conversion occurred (CENSOR = 0) or censoring occurred (CENSOR = 1).

12.PHARMACOKINETIC ANALYSES

Not applicable.

13. SAFETY ANALYSES

All safety analyses will be based on the Safety population. All available data as of the data cut-off will be used in the safety analyses.

13.1 Extent of Exposure and Compliance

Study drug exposure will be summarized for each INS-212 treatment arm and overall based on the total number of doses taken, the total number of doses missed, compliance and the duration of treatment. Number of doses taken, number of doses missed and compliance will be summarized by overall treatment period and by each visit (Month). Duration of treatment in months will be summarized for the 12-month treatment period. Duration of treatment is defined as the difference between the last dose date and the first dose date in INS-312 plus 1.

Study drug compliance will be calculated as follows:

- Compliance [%] = (Actual number of vials used)/(Prescribed number of vials to be used) ×100%
- Prescribed number of vials to be used = Number of days study medication is to be taken (based on the duration of treatment). At all visits, prescribed number of doses to be taken is the last visit date at that visit (month) minus the first visit date at that visit (month) minus 3 plus 1.
- The actual number of vial used is collected in the eCRF.

Study drug compliance will be summarized by INS-212 treatment arm and overall using counts and percentages as categorized below:

- >120%
- 80% ≤ compliance ≤120%
- <80%

13.2 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred on or after the date of first dose of study medication in INS-312 and within 28 days after the last dose. If it can't be determined whether the AE is treatment emergent due to a partial onset date, then it will be classified as treatment emergent. All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. At visits where study drug is administered, the occurrence of AEs will be assessed before and after administration of study drug. Any AE that has occurred before administration of the study drug on Day 1 in INS-312 and was resolved will be documented

for study INS-212. Verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA).

Each AE summary will be displayed by INS-212 treatment arm and overall. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of total incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs.
- Subject incidence of TEAEs and total number of TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of most common (≥5%) TEAEs and total number of TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of serious TEAEs and total number of serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs and of serious TEAEs adjusted for exposure by MedDRA system organ class and preferred term. Subject-years incidence will be computed as the number of subjects who experienced the event during the study divided by the cumulative number of years all subjects were active in the treatment arm. For those subjects in the study at the time of data base cutoff (as example, for DMC review), their years in study will be censored at the time of database cutoff. To adjust for per 1,000 subject-years of exposure, the resulting incidence rate will be multiplied by 1,000.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and common terminology criteria for adverse events (CTCAE) severity grade (i.e., 1 to 5). At each level of subject summarization, a subject is classified per the highest severity if the subject reported one or more events. AEs with missing CTCAE severity grade will be considered as having missing CTCAE severity grade.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as “Definitely”, “Probable”, or “Possibly”. At each level of subject summarization, a subject is classified per the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered as having missing relationship.
- Subject incidence of serious TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as “Definitely”, “Probable”, or “Possibly”. At each level of subject summarization, a subject is classified per the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered as having missing relationship.

- Subject incidence of TEAEs leading to death as an outcome by MedDRA system organ class and preferred term
- Exposure adjusted subject incidence of TEAEs leading to death as an outcome and by MedDRA system organ class and preferred term. Subject-years exposure adjusted incidence rate will be calculated the way it is described above.
- Subject incidence of TEAEs leading to study drug withdrawn and Multi-Drug Regimen for NTM withdrawn by MedDRA system organ class and preferred term.
- Subject incidence of serious TEAEs leading to study drug withdrawn and Multi-Drug Regimen for NTM withdrawn by MedDRA system organ class and preferred term.
- Time to first serious adverse event (SAE) by Treatment Arm will be summarized using Kaplan-Meier curves and estimates. Median time together with the 25th and 75th percentiles and associated 95% CI will be presented by treatment arm as well as the number and percentage of censored observations. Time will be censored at the date of last contact on or before EOS for each subject who didn't have any SAE. If there are insufficient SAEs only the summary table will be provided.

All information pertaining to AEs noted during the study will be presented in a subject listing. In addition, serious TEAEs, TEAEs leading to death and TEAEs leading to drug withdrawn will be shown in one or more separate subject listings.

13.3 Clinical Laboratory Evaluation

Laboratory parameters (hematology and chemistry) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to first dose of study drug in INS-312. Descriptive statistics at baseline and change from baseline is limited to continuous data. Laboratory parameters summary will be displayed by INS-212 treatment arm and overall.

Shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to each post-baseline visits. Reference ranges established by the central lab will be used to determine shifts. Determination of clinical significance for all out-of-range lab values will be made by the Investigator.

The numbers and percentages of subjects with clinically significant abnormal laboratory values will be summarized by each visit.

Clinical laboratory results will be provided in subject listings.

13.4 Vital Signs

Vital signs (body weight, BMI, blood pressure, pulse rate, body temperature, respiratory rate and oxygen saturation) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to first dose of study drug in INS-312. Vital sign parameters summary will be displayed by INS-212 treatment arm and overall.

All vital sign results will be shown in subject listings.

13.5 Physical Examination

Physical examination results will be included in subject listings only.

13.6 Audiology Test

Audiology (by each ear and frequency) will be summarized using descriptive statistics at baseline, Month 6 and Month 12 (EOT). Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to first dose of study drug in INS-312. Audiology test summary will be displayed by INS-212 treatment arm and overall.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes in the protocol-specified analyses are planned.

15.APPENDICES

15.1 Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (eg, μ, a, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.
- All outputs will be generated in the Rich Text Format file.

Tables

- Formal organization of tabulations may be changed during programming if appropriate, eg, tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.
- Means and medians will be presented to one more decimal place than the raw data. Standard deviations will be presented to two more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- Ratios (eg, hazard ratios) will be presented to two decimal places.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “lost to follow-up,” this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence limits should be presented to one decimal place more than the raw/derived data (ie, to the same number of decimal places as the mean).
- Percentiles (eg, 25%, 75%) should be presented to one decimal place more than the raw/derived data.
- For all inferential analyses, p-values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). P-values less than 0.0001 will be presented as “<0.0001”.
- The first footnote will be “Source: xxx”, where xxx indicates the source listing number(s) and/or source dataset(s).

Listings

- Formal organization of the listing may be changed during programming if appropriate, eg, additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints, etc.
- If not otherwise specified, all data listings will be sorted by treatment in INS-212, geographic region, subject number, visit, and date/time as appropriate.
- All date values will be presented in a SAS date (eg, 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (eg, 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.

Missing or incomplete dates and time (ie, AEs and concomitant medications)

The most conservative approach will be systematically considered. If the AE onset date is missing / incomplete, it is assumed to have occurred during the study treatment phase (ie, considered a TEAE) except if the partial onset date or other data such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment. For analyses purpose, all missing time will be replaced by 00:00 (HH:MM) using 24-hour clock.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as '01'.
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (eg, ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the dose of study drug or completely missing, the start date will be estimated to be the day of study drug dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts

of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to the last of the month (eg, ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (eg, ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug and will be imputed using the last known date on the study.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between one date (*date1*) and another later date (*date2*) is calculated using the following formula:

  duration in days = date2 – date1 + 1
- **Months** – A duration expressed in months is calculated as the number days divided by 365.25/12 (~30.4).
- **Years** – A duration expressed in years between one date (*date1*) and another later date (*date2*) is calculated using the formula noted below:
  duration in years = (date2-date1 (in days) +1)/365.25
- **Body Mass Index (BMI)** – BMI is calculated using height (cm) and weight (kg) using the following formula:
  BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2]
- **Change from baseline** – Change from baseline will be calculated as:
  Change = post baseline value – baseline value
- **Percent change from baseline** – Change from baseline will be calculated as:
  Percent change from baseline = (post baseline value – baseline value) / baseline value x 100

15.2 References

1. EQ-5D-3L User Guide, Version 5.1, April 2015. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-3L_UserGuide_2015.pdf