Statistical Analysis Plan

Insmed Incorporated

Protocol: INS-212

A Randomized, Open-Label, Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Subjects with Nontuberculous Mycobacterial (NTM) Lung Infections caused by Mycobacterium avium complex (MAC) that are refractory to treatment

Protocol Amendment # 3

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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
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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
ANCOVA	Analysis of Covariance
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EQ-5D	Formerly EuroQol 5D, a generic health-status classification instrument
ICH	International conference on harmonisation
IPD	Important Protocol Deviation
ITT	Intent to treat
LAI	Liposomal amikacin for inhalation
LS	Least Squares
MAC	Mycobacterium avium complex
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MNAR	Missing Not at Random
NTM	Nontuberculous mycobacteria
PK	Pharmacokinetic
PP	Per protocol
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Term
SGRQ	St. George's Respiratory Questionnaire
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WHO	World Health Organization

DEFINITIONS

Intent-to-Treat Population	The intent-to-treat (ITT) population is the set of all randomized subjects.
Per-Protocol Population	The per-protocol (PP) population will include all ITT subjects who received at least 1 dose of either LAI plus a multi-drug regimen or a multi-drug regimen, except those with important protocol deviations (IPDs). IPDs are those protocol deviations that are major in the sense that, alone or in combination, have the potential to influence the estimation of effect on efficacy outcomes, particularly the primary efficacy outcome. The IPDs will include deviations such as not meeting major entry criteria.
Safety Population	The safety population is the set of subjects who received at least 1 dose of LAI and subjects who randomized to the treatment of a multi-drug regimen alone. Subjects randomized to the treatment of a multi-drug regimen alone must have at least one dose of multi-drug regimen in this study.
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 AEs that occurred on or after the date of first dose of study medication and within 28 days after the last dose.

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented during the analyses of data collected within the scope of Insmed Incorporated Protocol INS-212 [A Randomized, Open-Label, Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Subjects with Nontuberculous Mycobacterial (NTM) Lung

Infections caused by Mycobacterium avium complex (MAC) that are refractory to treatment]. This SAP was developed per SynteractHCR standard operating procedure BIO-0202-SOP-01.0 and the SynteractHCR SAP template.

This SAP is based on:

- Protocol INS-212, Amendment # 3, dated 22 February 2016
- International Conference on Harmonization (ICH) guidance E9 (Statistical Principles for Clinical Trials)

All decisions regarding final analyses, including SAP finalization, will be approved by the Sponsor and placed on file prior to the last subject reaching the Month 6 visit. Deviations from the final approved plan will be noted in the clinical study report (CSR).

2. STUDY OBJECTIVES

This Statistical Analysis Plan (SAP) describes the evaluation of effects of LAI [590 mg] administered QD when added to a multi-drug regimen, compared to a multi-drug regimen alone. The SAP describes an initial set of analyses that, if favorable, would be the basis for submissions to regulatory authorities for 'accelerated approval' (in the US) and potentially 'conditional approval' (in the EU). The SAP also describes a latter set of analyses that will be used by regulatory authorities to determine whether 'full regulatory approval' would be granted to permit continued marketing of LAI. No multiplicity adjustment is provided for these separate primary objectives since both objectives must be met for continued marketing of LAI.

In the initial set of analyses, the primary objective is an assessment of effects on achieving culture conversion by Month 6; in the latter set of analyses, the primary objective is an assessment of effects on the durability of treatment success as assessed 3 months after the end of total treatment course (negative sputum culture after 3 months off treatment). At the initial and latter sets of analyses, secondary objectives will be assessed in a hierarchical order, as described in this SAP. If a discrepancy occurs between protocol and SAP, the hierarchy as described in the SAP will take precedence.

2.1 Primary Objectives

The primary objective at the initial set of analyses is to evaluate the microbiological effect of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, for achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6.

The primary objective at the latter set of analyses is to evaluate the microbiological effect of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, on the durability of treatment success as assessed 3 months after the end of total treatment course (negative sputum culture after 3 months off treatment).

2.2 Secondary Objectives

The secondary objective at the initial set of analyses is to evaluate the effect of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, on measures that contribute insights about the clinical relevance for early microbiological success. These include the following secondary endpoints that will be assessed in a hierarchical manner:

2. Six-minute walk test (6MWT) at Month 6.
3. Time to culture conversion
4. Change from baseline (Day 1) in quality of life scores on the St. George's Respiratory Questionnaire (SGRQ) at Month 6.

The secondary objectives at the latter set of analyses are to evaluate the effect of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, on the following secondary endpoints that will be assessed in a hierarchical manner:

5. Achieving sustainability (consecutive negative sputum cultures [with no more than 2 consecutive monthly broth positive cultures] for 12 months on treatment)
6. The 6MWT at end of treatment (EOT)

To protect the integrity of the evaluation of the primary and secondary objectives that will be assessed at the latter set of analyses, the data for these objectives will remain confidential at the time of the initial set of analyses.

2.3 Exploratory Objectives

The exploratory objectives at the initial set of analyses will be to assess the following exploratory endpoints, to be performed in a descriptive manner:

1. The change from Baseline to Month 6 in the 6MWT for converters versus non-converters within the LAI (590 mg) administered QD added to a multi-drug regimen arm

2. The change from Baseline to Month 6 on the 6MWT for converters versus non-converters for all subjects
3. The change from Baseline to Month 6 on the 6MWT for converters versus non-converters within the multi-drug regimen alone arm
4. The change from Baseline to Month 6 on Body Mass Index (BMI), comparing those randomized to LAI (590 mg) administered QD when added to a multi-drug regimen vs. those randomized to a multi-drug regimen alone
5. Subject reported symptoms of NTM and change from baseline (Day 1) in quality of life scores on the SGRQ – Part 2 (Activities of Daily Living) at Month 6, comparing those randomized to LAI (590 mg) administered QD when added to a multi-drug regimen vs. those randomized to a multi-drug regimen alone
6. The change from baseline (Day 1) in the EQ-5D-3L subject reported health outcomes at Month 6, comparing those randomized to LAI (590 mg) administered QD when added to a multi-drug regimen vs. those randomized to a multi-drug regimen alone.

The exploratory objectives at the latter set of analyses will be to compare those randomized to LAI (590 mg) administered QD when added to a multi-drug regimen vs those randomized to a multi-drug regimen alone, with regarding to the following exploratory endpoints, to be performed in a descriptive manner:

7. The 6MWT at Month 8 and 3 months off treatment
8. The proportion of subjects achieving culture conversion with durability after 12 months off treatment (end of study [EOS])
9. Change from baseline (Day 1) in the EQ-5D-3L subject reported health outcomes at EOT
10. At EOS the number of subjects who develop a new strain of MAC during the study
11. All-cause mortality 12 months after treatment (EOS).

2.4 Safety Objective

The safety objective is to evaluate the safety and tolerability of LAI (590 mg) QD added to a multi-drug regimen arm.

2.5 Pharmacokinetic Objectives

1. The pharmacokinetic (PK) objective is to evaluate the PK of LAI via a population PK approach (Months 1, 3 and 6).
2. To evaluate the concentration of amikacin in sputum after 2 days interruption of LAI dosing in a subset of subjects (Months 4, 5 and 6)
3. To evaluate the concentration of amikacin in sputum after 28 days off-LAI in a subset of subjects
4. To evaluate the concentration of amikacin in sputum after 3 months off-LAI in a subset of subjects

2.6 Comprehensive Pharmacokinetic Sub-Study Objectives

1. To characterize systemic amikacin exposure, including approximate systemic bioavailability in Japanese subjects, using a population PK model to describe the disposition of amikacin in the serum
2. To compare population PK modeling between Japanese subjects to historical population PK modeling for LAI
3. To explore the amikacin concentration in sputum in Japanese subjects

2.7 CT Scan Sub-Study Objective

1. To compare assessments of chest CT scans, read by a trained medical professional, from Baseline (Day 1) to EOT in a subset of subjects within each treatment arm

3. STUDY DESIGN AND PLAN

The Screening window (10-14 weeks) allows time for sputum culture results, susceptibility by minimum inhibitory concentration (MIC) determination, and scheduling of Screening assessments. Once Screening assessments are complete and sputum culture

results are known, eligible subjects will be randomized 2:1 to LAI administered QD plus a multi-drug regimen or a multi-drug regimen alone.

At the initial set of analyses, the primary efficacy endpoint is the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 in the LAI plus a multi-drug regimen arm compared to a multi-drug regimen alone.

Converters are defined as subjects who have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. After culture conversion, relapse or recurrence is defined as having MAC-positive sputum cultures in liquid broth media (agar negative) for 3 or more consecutive months, or having 1 MAC-positive sputum culture on solid media (agar positive). Non-converters are defined as subjects who do not have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study (see Protocol Section 4.6).

Sputum culture results will only be available to the site after the Month 6 sputum result is known, in time for the Month 8 visit. At Month 8 (-28 to +7 days), after all sputum culture results are known, up to and including Month 6, subjects will be assessed as converters or non-converters.

All converters will remain on their randomized regimen in Study INS-212. All converters who, after culture conversion, subsequently have MAC-positive sputum cultures in liquid broth media (agar negative) for 1 or 2 consecutive months only, will also remain on their randomized regimen in Study INS-212. All converters will continue on their randomized treatment regimen until they complete a total of 12 months of treatment, starting from the first of 3 consecutive negative cultures that defines culture conversion. These subjects will return after the end of treatment (EOT) visit for 28 day, 3, 6 and 12 months off-treatment follow-up visits. The 12 months off-treatment follow-up visit will be the EOS visit. No NTM treatment will be administered during the off-treatment phase.

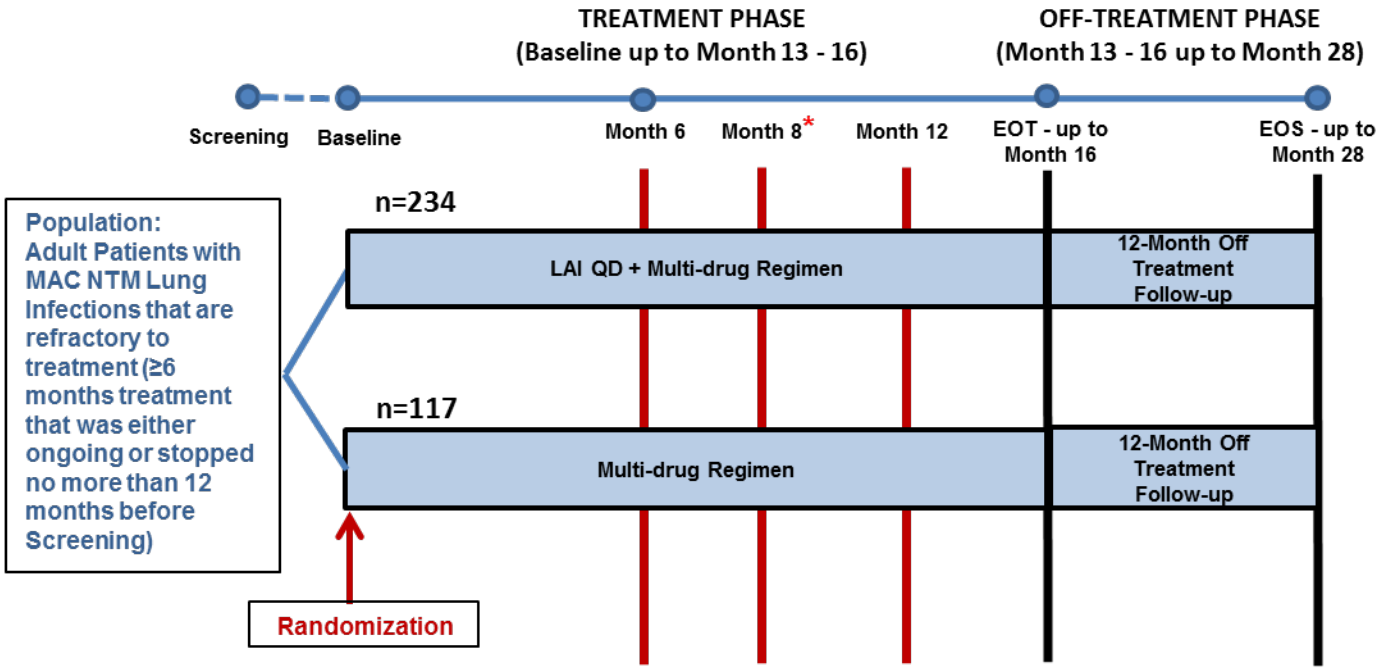
At Month 8, all non-converters will exit INS-212. All subjects who experienced a relapse or recurrence after culture conversion by Month 6 will exit INS-212 at their Month 8 visit. These subjects maybe eligible to enter a separate open-label study of LAI (Study INS-312), provided all entry criteria have been met for that study. Any subject who discontinues prior to Month 8 or does not enter INS-312 will be followed up to 12 months off study drug.

Expectorated sputum (spontaneous or induced e.g., with nebulized hypertonic saline solution as needed) will be collected at Day 1 and every month through Month 6, at Month 8, Month 12, EOT, and at 28 days, 3, 6, and 12/EOS months off treatment.

All subjects will be seen monthly for routine visits through Month 6, at Month 8, 10, 12, 14, EOT, and at 28 days, 3, 6 and 12/EOS months off treatment. Unscheduled visits will occur as needed should subject's symptoms worsen between visits.

Figure 1: Study Design

Figure 1 shows a schematic of the study design.



*All converters (at least 3 consecutive monthly negative sputum cultures by Month 6) without relapse or recurrence will remain in study for 12 months, starting from the first negative culture that defines culture conversion.
*All non-converters and subjects who experienced a relapse or recurrence after culture conversion by Month 6 will discontinue the study at Month 8 and may be eligible to enter a separate Open-Label study (INS-312).

4. SCHEDULE OF EVENTS

The schedule of assessments is displayed in Table 2.

Table 2: Schedule of Events

INS-212		TREATMENT PHASE												OFF-TREATMENT PHASE			
	Screening	Baseline	Month 1[a]	Month 2[a]	Month 3	Month 4	Month 5[a]	Month 6	Month 8	Month 10	Month 12	Month 14	EOT up to Month 16	28 Day Safety Follow-Up	3 Month Safety Follow-Up	6 Month Safety Follow-Up	EOS (12 Month Safety Follow-Up)
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)	(V15)	(V16)	(V17)
Visit Window	Approximately -98 to -70 (10-14 weeks)[b]	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(-28; +7)	(±5)	(±5)	(±5)	(±5)	(±5)	(±7)	(±7)	(±7)
Informed consent	X	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pregnancy test[c]	X	X	X	X	X	X	X	X	X	–	X	–	X	–	–	–	-
ECG	X	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–
SGRQ	–	X	–	–	X	–	–	X	X	–	X	–	X	–	X	–	-
EQ-5D-3L	–	X	–	–	X	–	–	X	X	–	X	–	X	–	X	–	-
Medical history	X		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Physical examination	X	X			X	X		X	X	–	X	–	X	–	X	–	X
Vital signs and pulse oximetry	X	X[d]			X[d]	X[d]		X[d]	X[d]	–	X[d]	–	X	–	X	–	X
6 minute walk test[e]	–	X	–	–	–	X	–	X	X	–	–	–	X	–	X	–	-

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INS-212		TREATMENT PHASE												OFF-TREATMENT PHASE			
	Screening	Baseline	Month 1[a]	Month 2[a]	Month 3	Month 4	Month 5[a]	Month 6	Month 8	Month 10	Month 12	Month 14	EOT up to Month 16	28 Day Safety Follow-Up	3 Month Safety Follow-Up	6 Month Safety Follow-Up	EOS (12 Month Safety Follow-Up)
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)	(V15)	(V16)	(V17)
Visit Window	Approximately -98 to -70 (10-14 weeks)[a]	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(-28; +7)	(±5)	(±5)	(±5)	(±5)	(±5)	(±7)	(±7)	(±7)
Pulmonary Function Tests[f] (FEV_1[L], $FEF_{(25-75\%)}$, FVC)	–	X	–	–	–	–	–	X	–	–	–	–	–	–	–	X	–
Audiology test	X[g]		–	–	X	–	–	X	–	–	X	–	X	–	–	–	–
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Care Resource Utilization	–	X	X	X	X	X	X	X	X	–	X	–	X	–	–	–	–
AE assessment	–	X[h]	X	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	X	X
Chemistry	X	X	X	–	X	–	–	X	X	–	X	–	X	–	–	–	–
Hematology	X	X	X	–	X	–	–	X	X	–	X	–	X	–	–	–	–
Urinalysis	X	X	X	–	X	–	–	X	X	–	X	–	X	–	–	–	–

INS-212		TREATMENT PHASE												OFF-TREATMENT PHASE			
	Screening	Baseline	Month 1[a]	Month 2[a]	Month 3	Month 4	Month 5[a]	Month 6	Month 8	Month 10	Month 12	Month 14	EOT up to Month 16	28 Day Safety Follow-Up	3 Month Safety Follow-Up	6 Month Safety Follow-Up	EOS (12 Month Safety Follow-Up)
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)	(V15)	(V16)	(V17)
Visit Window	Approximately -98 to -70 (10-14 weeks)[c]	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(-28; +7)	(±5)	(±5)	(±5)	(±5)	(±5)	(±7)	(±7)	(±7)
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 (Japan)	See APPENDIX 5: JAPAN SPECIFIC CT SCAN SUB-STUDY																
Sub-Set: Population PK sampling[j] (blood and sputum)	–	–	X	–	X	–	–	X	–	–	–	–	–	–	–	–	–
Sub-Set: Sputum only PK Collection	–	X	–	–	–	X	X	X	–	–	–	–	–	X	X	–	–
Sub-Study: Comprehensive PK sampling[k] (Japan)	X		X	–	X	–	–	X	–	–	–	–	–	–	–	–	–

INS-212		TREATMENT PHASE												OFF-TREATMENT PHASE			
	Screening	Baseline	Month 1[a]	Month 2[a]	Month 3	Month 4	Month 5[a]	Month 6	Month 8	Month 10	Month 12	Month 14	EOT up to Month 16	28 Day Safety Follow-Up	3 Month Safety Follow-Up	6 Month Safety Follow-Up	EOS (12 Month Safety Follow-Up)
	(V1)	(V2)	(V3)	(V4)	(V5)	(V6)	(V7)	(V8)	(V9)	(V10)	(V11)	(V12)	(V13)	(V14)	(V15)	(V16)	(V17)
Visit Window	Approximately -98 to -70 (10-14 weeks)[b]	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(-28; +7)	(±5)	(±5)	(±5)	(±5)	(±5)	(±7)	(±7)	(±7)
Send sputum collection containers home	X	X	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	–		–	–	–	–
Dispense study drug[l]	–	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	–	–	–	–
Start consent process for INS-312								X[m]									

Note: At visits where study drug is administered, all patient-reported outcomes, 6MWT, Physical Exam should be performed before study drug administration.
Note: Culture conversion is defined to occur when the first of 3 consecutive monthly sputum cultures are MAC negative. All NTM treatment will stop when a subject has completed 12 months of treatment starting from their first of 3 negative cultures when they were defined as a 'converter'.
Abbreviations: AE, adverse event; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; ED-5D-3L, EuroQol 5D; $FEF_{(25-75\%)}$, forced expiratory flow at 25-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PK, pharmacokinetic; 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] The Screening window allows time for sputum culture results, minimum inhibitory concentration (MIC) determination, and scheduling of Screening assessments. Any delay in obtaining microbiological results and MICs must be reported to the Sponsor immediately and documented within the study source documents. In the event that sputum culture results are not known by 8 weeks (Day -14), the Baseline (Day 1) visit should be scheduled as soon as possible in order to maintain the Screening window, and an extension of the Screening window to 14 weeks is allowed, if necessary. If sputum culture results are known prior to 8 weeks (Day -14), the Screening window of 10 weeks must be maintained.
[c] Serum pregnancy testing will be performed on women of child bearing potential at Screening. A urine pregnancy will test will be performed on women of child bearing potential at all other visits. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
[d] Vital signs and pulse oximetry will be assessed both before and after dosing on visits where study drug is administered.
[e] The 6MWT must be conducted by a site member who is blinded to the subject's open-label treatment assignment.
[f] The PFTs will be performed at sites with access to spirometers and trained personnel to perform spirometry tests. See Section 7.2.4.
[g] The Baseline audiology examination must be performed during Screening period or on Day 1 before study drug administration.
[h] At Baseline (Day 1), AEs will be assessed only after study drug administration or first dose of multi-drug regimen. Any AE that has occurred prior to the first dose must be included in the subject's medical history, including any AEs that occur within the Screening period.
[i] Only for subjects who agreed to participate in the CT Scan sub-study. A prior chest CT scan may be used as a subject's Baseline (Day 1) measurement if this CT scan was obtained within 6 months from the subject's Baseline (Day 1) visit. Subjects will have their 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 4 for additional details on the CT Scan sub-study.
[j] Only for subjects who agreed to participate in the population PK sub-set (US and Japan only). Blood and sputum samples will be collected from 0 to 1 hours before and from 1 to 4 hours after study drug administration (Section 7.4.1).
[k] Only for Japanese subjects from sites in Japan who agreed to participate in the comprehensive PK sub-study. Please refer to APPENDIX 5 for additional details on the comprehensive PK sub-study.
[l] Study drug will be dispensed to all subjects up to and including the Month 6 visit. At Month 8, subjects who are non-converters or experienced a relapse or recurrence after achieving culture conversion will exit the study at Month 8/EOT visit (Section 3.1, Section 4.6). Subjects who remain in the study after Month 8 will receive study drug for 12 months beginning from the first of 3 negative cultures that defines culture conversion.
[m] If Study INS-312 has been IRB/EC approved, start the ICF consent process at Month 6, in order to provide sufficient time for the subject to make an informed decision

5. DISCUSSION OF STUDY DESIGN

5.1 Number of Subjects

The study is designed to enroll enough subjects to ensure at least 261 evaluable subjects reach Month 6. Accounting for discontinuation, it is anticipated that up to approximately 351 randomized subjects may be required.

5.2 Study Duration

This study has an anticipated recruitment period of 18-24 months, with each subject receiving treatment in the study for up to 16 months (excluding Screening and observational follow-up). Subjects will remain in the study for up to 31 months: approximately 2.5 months for Screening, plus up to 16 months in the randomized open-label treatment phase, plus 12 months in the off-treatment phase.

5.3 Assignment to Study Drug

Eligible subjects will be stratified at Screening according to smoking status (current smoker or not) and prior multi-drug regimen (on treatment or off treatment for at least 3 months) and then randomly assigned in a 2:1 ratio to treatment with either LAI (590 mg) QD plus multi-drug regimen or to multi-drug regimen alone, using an interactive web response system. Treatment randomization codes will be generated using SAS®.

5.4 Data Monitoring Committee

In order to ensure the safety of subjects enrolled in INS-212, 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

The sample size was determined for the primary comparison between the treatment arms LAI plus a multi-drug regimen and a multi-drug regimen alone with respect to the proportion of subjects achieving culture conversion by Month 6 using nQuery Advisor® 7.0. Assuming a culture conversion rate by Month 6 of no less than 20% for the LAI plus a multi-drug regimen treatment arm, the rate by Month 6 of 5% for the multi-drug regimen alone treatment arm, and a 2:1 randomization ratio, a sample size of 261 subjects (174 for LAI plus a multi-drug regimen and 87 for the multi-drug regimen) will provide at least 90% power for the continuity corrected Chi-square test at the 2-sided significance level of 0.05.

The sample size was also evaluated for the secondary endpoint of change from baseline to Month 6 in 6 Minute Walk Distance (6MWD). Assuming a common standard deviation of 100 and a 2:1 randomization ratio to either LAI plus a multi-drug regimen or a multi-drug regimen alone, a sample size of 192 subjects (128 for LAI plus a multi-drug regimen and 64 for the multi-drug regimen) will provide at least 90% power to detect a between-treatment difference of 50 meters in mean change from baseline to Month 6 in 6MWD using a two arm t-test at the 2-sided significance level of 0.05.

Due to lack of durability data, it is difficult to estimate the power with a total sample size of 261 subjects for the comparison between treatment arms with respect to the proportion of subjects achieving culture conversion with durability after 3 months off treatment. Assuming the proportion of subjects achieving culture conversion with durability is 16% and 4% for LAI plus a multi-drug regimen and a multi-drug regimen respectively, and a 2:1 randomization ratio, a sample size of 261 subjects (174 for LAI plus a multi-drug regimen and 87 for the multi-drug regimen) will provide at least 83% power for the Pearson Chi-square test at the 2-sided significance level of 0.05.

6.2 Randomization and Blinding

Eligible subjects will be randomized 2:1 to open-label treatment with LAI plus a multi-drug regimen or a multi-drug regimen alone. Randomization will be stratified by smoking status (current smoker or not) and current multi-drug regimen (on treatment or off treatment for at least 3 months) at screening. The study is open-label.

7. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures. The ICH numbering convention will be used for all outputs. Unless otherwise noted, all statistical testing 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. Protection of the overall alpha at 0.05 is discussed in Section 10.7.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums, and by clinically relevant discretizations. 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 analysis set and treatment arm. 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 round-off 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 site, treatment 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. 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 Intent-to-Treat Population

The intent to treat (ITT) population is the set of all randomized subjects. Subjects will be classified according to their assigned treatment.

8.2 Per-Protocol Population

The per-protocol (PP) population will include all ITT subjects who received at least 1 dose of either LAI plus a multi-drug regimen or a multi-drug regimen, except those with important protocol deviations (IPDs). IPDs are those protocol deviations that are major in the sense that, alone or in combination, have the potential to bias efficacy, particularly the primary efficacy outcome. The IPDs will include deviations such as not meeting major entry criteria.

8.3 Safety Population

The safety population is the set of subjects who received at least 1 dose of LAI and subjects who randomized to the treatment of a multi-drug regimen alone. Subjects randomized to the treatment of a multi-drug regimen alone must have at least one dose of multi-drug regimen in this study.

9. STUDY POPULATION

9.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment arm. Summaries will include: the number of randomized subjects, the number of subjects in each analysis 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 primary efficacy conclusions of the study will be identified prior to database lock. Then the final determination of a subject excluded from the PP population will be made by the sponsor representative—also prior to database lock.

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

Major protocol deviations will be summarized by deviation category (i.e. compliance, prohibited medication, etc.) and treatment arm.

9.3 Demographic and Baseline Characteristics

Demographic variables include: country, consent to PK samples, age, sex, ethnicity and race. Age will be calculated in years relative to the informed consent date. Demographic variables will be summarized by region and overall.

Other baseline characteristics include: eligibility and stratification criteria. Descriptive statistics will be presented for age. Frequency counts and percentages will be presented for region, country, consent to PK samples, sex, ethnicity, race and stratification criteria. Demographic and baseline characteristics will be summarized for the ITT, Safety and PP populations.

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

Subjects excluded from the ITT, safety and PP population will be listed as well.

9.4 Medical History and Medical Conditions Present at Entry

Medical History data will be collected in Medical History eCRF page. For all non-serious adverse events (AEs) that occur between the time subject signs the informed consent form for the study and the time when subject receives his/her first dose 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 Prior and Concomitant Medications

Non-study medications taken 18 months prior to study treatment and during the study will be recorded. They will each be mapped to an Anatomical/Therapeutic/Chemical (ATC) class and Preferred Name using the World Health Organization (WHO) Drug Dictionary.

Concomitant medications are those medications taken on or after the first dose of study drug. Prior medications are those medications taken before the first dose of study drug. A medication that starts prior to first dose but continues after the first dose of study drug is classified both in prior and concomitant medications. Prior and concomitant medications will be summarized separately.

Concomitant medications will be summarized for each treatment by WHO 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. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT population. Additional supportive analyses of the primary efficacy endpoint at the initial analysis, (i.e., proportion of subjects achieving culture conversion by Month 6), and the primary efficacy endpoint at the latter analysis, (i.e., proportion of subjects achieving culture conversion with durability at 3 months off treatment), and the secondary endpoint 6MWD (change from baseline to Month 6 in 6MWT distance) also will be performed for the PP population.

There will be two separately timed sets of analyses. The first set of analyses, if favorable, would be the basis for submissions to regulatory authorities for ‘accelerated approval’ (in the US) and potentially ‘conditional approval’ (in the EU). In these analyses, the primary endpoint (proportion of subjects achieving culture conversion by Month 6) and the secondary endpoint (change from baseline to Month 6 in 6MWT distance) will be evaluated once the last subject has completed their Month 6 visit and

data for all subjects who have completed Month 6 are available. The second set of analyses will be used by regulatory authorities to determine whether 'full regulatory approval' would be granted and whether to permit continued marketing of LAI. In these analyses, the primary endpoint (proportion of subjects achieving culture conversion with durability at 3 months off treatment) and several pre-specified secondary endpoints will be evaluated when long term data are available. These secondary endpoints will be tested in a hierarchical order.

10.1 Efficacy Endpoints

Primary Efficacy at the Initial Analysis:
Each subject in the ITT population is classified as either a converter or non-converter. The primary efficacy endpoint is the proportion of subjects achieving culture conversion by Month 6.

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

This primary efficacy analysis will occur once the last subject has completed his/her Month 6 visit and data for all subjects who have completed Month 6 are available.

Secondary Efficacy at the Initial Analysis:
The secondary endpoints (6MWD at Month 6), time to culture conversion and SGRQ at Month 6 will be assessed at the initial analysis of the trial. These additional secondary endpoints will be assessed in a hierarchical manner.

7. **6MWD at Month 6:** The 6MWD is the distance walked in 6 minutes. The endpoint is the change from baseline to Month 6 in actual 6MWD.
2. **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 time to culture conversion is defined as the difference between the date of conversion and the date of first dose of study drug (i.e., (Date of conversion – Date of first dose) in days + 1 day). For subjects not achieving culture conversion by Month 6, time to 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).

3. **St. George's Respiratory Questionnaire (SGRQ):** The endpoint is the change from baseline to Month 6 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.

Exploratory Efficacy at the Initial Analysis:
At this analysis, all other endpoints that are defined to use data only during the first 6 months post randomization will be assessed and presented descriptively:

1. **BMI at Month 6:** The endpoint is the change from baseline to Month 6 in BMI.
2. **Subject reported symptoms of NTM:** The incidence of subjects who reported symptoms of NTM and change from baseline (Day 1) in quality of life scores on the SGRQ – Part 2 (Activities of Daily Living) at Month 6.
3. **EQ-5D-3L:** The change from baseline (Day 1) in the EQ-5D-3L subject reported health outcomes at Month 6.

Primary Efficacy at the Latter Analysis:
This endpoint is the proportion of subjects achieving culture conversion with durability, defined as achieving culture conversion by Month 6 and then having no more than 2 consecutive broth positive cultures) and no Agar positive culture up to 3 months off treatment. Converters with missing broth or Agar sputum culture result after Month 6 up to 3 months off treatment will be considered as not achieving culture conversion with durability except those subjects who are unable to produce sputum despite reasonable efforts, as reported by source documentation. Subjects who have relapse/recurrence, have "rescue" medication and/or die before reaching 3 months off treatment will be considered as not achieving culture conversion with durability.

A separate analysis for culture conversion with durability at 3 months off-treatment will be performed similarly as described above. In this analysis, those converters with no

more than 1 missing broth or Agar culture result after Month 6 will be considered as converters with durability at 3 months off-treatment and included in the numerator.

An additional analysis for culture conversion with durability at 3 months off-treatment will be performed in which the culture conversion with durability at 3 months off-treatment is defined as (1) achieving culture conversion by Month 6, (2) having neither broth nor Agar positive culture from culture conversion up to 3 months off-treatment, and (3) having no missing broth or Agar culture results (including missing culture results due to subject inability to produce sputum despite reasonable efforts).

Secondary Efficacy at the Latter Analysis:
The secondary endpoints to be assessed at the latter analysis of the trial will be assessed in a hierarchical manner:

1. **Culture conversion with sustainability:** The endpoint is the proportion of subjects achieving culture conversion with sustainability at EOT, defined as achieving culture conversion by Month 6 and then having no more than 2 consecutive broth positive cultures and no Agar positive culture up to EOT. Converters with missing broth or Agar sputum culture result at Month 8, 12, and/or EOT will be considered as not achieving culture conversion with sustainability. This excludes subjects who are unable to produce sputum despite reasonable efforts, as reported by source documentation. Subjects who have relapse/recurrence, have "rescue" medication and/or die before reaching EOT will also be considered as not achieving culture conversion with sustainability.

   A separate analysis for culture conversion with sustainability will be performed similarly as described above. In this analysis, those converters with no more than 1 missing broth or Agar culture result after Month 6 will be considered as converters with sustainability, and included in the numerator.

2. **6MWD at EOT:** The endpoint is the change from baseline to EOT in actual 6MWD.

3. **St. George's Respiratory Questionnaire (SGRQ):** The endpoint is the change from baseline to EOT 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. The SGRQ is completed at baseline and at Months 3, 6, 8, 12, and at EOT and 3 months off treatment visit.

To protect the integrity of the evaluation of the primary and secondary objectives that will be assessed at the latter set of analyses, the data for these objectives will remain confidential at the time of the initial set of analyses.

Exploratory Efficacy at the Latter Analysis:
At this analysis, the following endpoints will be assessed and presented descriptively:

1. **6MWD at Month 8:** The endpoint is the change from baseline to Month 8 in actual 6MWD.
2. **6MWD at 3 Months off treatment:** The endpoint is the change from baseline to 3 months off treatment in actual 6MWD.
3. **Culture conversion with durability after 12 months off treatment (EOS):** The endpoint is the proportion of subjects achieving culture conversion with durability, defined as achieving culture conversion by Month 6 and then having no more than 2 consecutive broth positive cultures) and no Agar positive culture up to EOS. Converters with missing broth or Agar sputum culture result after Month 6 up to EOS will be considered as not achieving culture conversion with durability at EOS except those subjects who are unable to produce sputum despite reasonable efforts, as reported by source documentation. Subjects who have relapse/recurrence, have "rescue" medication and/or die before reaching EOS will be considered as not achieving culture conversion with durability at EOS.
4. **EQ-5D-3L:** 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 (UK) 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

5. **New strain of MAC:** The incidence of subjects who achieve culture conversion and then develop a new strain of MAC during the study will be summarized.
6. **CT scan:** Radiological changes in CT scan at EOT. The findings of CT scan at EOT will be recorded as "Improved", "Worsened" and "No change from previous scan" in source data.
7. **Mortality:** The endpoint is time to death (all-cause mortality) through EOS. Live subjects will be censored at the date of last contact or at EOS (whichever is earlier).

10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of study drug. 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. For LAI arm, if first dose of the study drug could not be identified (missing), visit 2 (Day 1) will be considered as baseline. For multi-drug regimen alone arm, visit 2 (Day 1) will be considered as baseline.

10.3 Adjustments for Covariates

The corresponding baseline value will be used as covariate for efficacy endpoints 6MWD, SGRQ and EQ-5D analyzed using the mixed model repeated measures (MMRM) method as described in Section 11.2.

10.4 Handling of Dropouts or Missing Data

The handling of missing sputum culture results is built into the determination of whether or not a subject achieves culture conversion, culture conversion with sustainability, and

culture conversion with durability. For each endpoint, all subjects will be classified as either a converter or a non-converter. Please refer to Section 10.1 for details.

Missing data will not be imputed for any endpoints other than for the primary and supportive analyses of 6MWD. For the primary analysis, change from Baseline to Month 6 in 6MWD will be analyzed assuming Missing-Not-at-Random (MNAR) using a model under the pattern-mixture model framework and missing data will be multiply imputed. Please refer to Section 11.2 for details. For the supportive analysis, change from Baseline to Month 6 in 6MWD will be analyzed for PP and ITT using LOCF. Please refer to Section 11.2 for detail.

10.5 Data Monitoring

Safety data will be monitored periodically, which has been outlined in DMC Charter. There would be no plans to adjust the final critical value as a result of these analyses and there is no intention of stopping the trial on the basis of any such information.

10.6 Examination of Subgroups

No formal subgroup comparisons between the two treatment groups with respect to the primary endpoint are planned. However, exploratory, subgroup analyses may be performed to evaluate potential heterogeneity in treatment benefits.

10.7 Multiple Comparisons and Multiplicity

The superiority of the treatment of LAI plus a multi-drug regimen relative to the multi-drug regimen alone is assessed at the two-sided 0.05 level. As noted in sections 2 and 10, at the initial set of analyses, hierarchical methods are specified to address multiplicity across endpoints. The same approach has been specified at the latter set of analyses.

As noted in Sections 2 and 10, the initial set of analyses, if favorable, would be the basis for submissions to regulatory authorities for ‘accelerated approval’ (in the US) and potentially ‘conditional approval’ (in the EU), while the latter set of analyses that will be used by regulatory authorities to determine whether ‘full regulatory approval’ would be granted and whether to permit continued marketing of LAI. No multiplicity adjustment is provided for these dual primary objectives since both objectives must be met for continued marketing of LAI.

10.8 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

At the initial set of analyses, the formal analyses of the primary endpoint (i.e., the proportion of subjects achieving culture conversion by Month 6) and of the secondary endpoints (i.e., the change from baseline to Month 6 in 6MWT, Time to conversion, and SGRO) will be performed after the last subject completes Month 6 and the Month 6 sputum culture result and 6MWT distance data are available for the analyses. At the latter set of analyses, the formal analyses of the primary endpoint (i.e., durability of culture conversion) will be performed after the last subjects completes 3-months follow-up after the end of total treatment course.

Unless otherwise stated, the ITT population will be used for all efficacy analyses.

11.1. Culture Conversion by Month 6:

At the initial set of analyses, the primary efficacy endpoint is the proportion of subjects achieving culture conversion by Month 6. Culture conversion by Month 6 is defined in Section 10.1. The proportion of subjects achieving culture conversion by Month 6 will be analyzed using the Cochran-Mantel-Haenszel test, stratified by smoking status and prior multi-drug regimen. The treatment comparison will be tested at two-sided significance level of 0.05. The null hypothesis assumes that culture conversion by Month 6 is independent of treatment, and the alternative hypothesis assumes that culture conversion by Month 6 is associated with treatment.

The following lines provide sample SAS code for the Cochran-Mantel-Haenszel test:

```
PROC FREQ DATA= INPUT_DATA;
TABLES BSPMS*TRT*RSP / CMH;
```

BSPMS is the combination of smoking status and prior multi-drug regimen (with 4 levels: Yes/Yes, Yes/No, No/Yes, and No/No), TRT is treatment and RSP is the response (Yes or No) of culture conversion at Month 6. The adjusted odds ratio (LAI added to multi-drug regimen / multi-drug regimen alone), its 95% confidence interval (CI) and p-value will be presented.

The primary efficacy analysis will be performed for the ITT population. As a supportive analysis, this same analysis of the primary efficacy endpoint will be performed using the PP population.

11.2 6MWD:

The analysis of change from Baseline to Month 6 in 6MWD will be performed for the ITT population (assuming MNAR) using a model under the pattern-mixture model framework. This model assumes that subjects on the LAI plus a multi-drug regimen arm with missing data follow the response distribution of a multi-drug regimen alone arm. It involves 3 steps:

1. The posterior mean and covariance estimates from the SAS MI procedure using the available non-missing data of a multi-drug regimen alone arm will be utilized to multiply impute missing data for both treatment arms.

2. The endpoint will then be analyzed for each complete data set with imputed data using an analysis of covariance (ANCOVA) with treatment arm and the randomization strata as factors, and the Baseline 6MWD as a covariate.

3. The treatment least-squares (LS) mean differences will be averaged and the associated standard errors will be summarized based on within-imputation and between-imputation variance using the SAS MIANALYZE procedure, to yield a final estimate of treatment contrast with associated 95% CI and p-value.

As sensitivity analysis, the change from Baseline to Month 6 in 6MWD will be analyzed using an MMRM analysis over Months 4 and 6 for the ITT population. The MMRM will include treatment, month, the treatment-by-month interaction, combination of smoking status and prior multi-drug regimen (with 4 levels: Yes/Yes, Yes/No, No/Yes, and No/No) as fixed factors, the baseline 6MWD as a covariate and the baseline 6MWD-by-month interaction. The denominator degrees of freedom for error will be estimated using the method of Kenward-Rogers. An unstructured covariance matrix will be used for the MMRM. The between-treatment difference in least squares (LS) mean change from baseline to Month 6, the corresponding 95% CI for the true between-treatment difference, and the p-value will be presented.

The following lines provide sample SAS code for the MMRM analysis:

```
PROC MIXED DATA = INPUT_DATA METHOD = REML;
  CLASS PATIENT TRT MONTH BSPMS;
  MODEL CHG = BSPMS TRT MONTH BASE TRT*MONTH MONTH*BASE
              /DDFM=KR;
  REPEATED MONTH / SUBJECT = PATIENT TYPE = UN;
  LSMEANS TRT*MONTH / SLICE=MONTH DIFF ALPHA=0.05 CL;
```

BSPMS is the combination of smoking status and prior multi-drug regimen, TRT is treatment, MONTH is the scheduled visit, and BASE is the baseline 6MWD.

A supportive ANCOVA analysis of the change from Baseline to Month 6 in 6MWD with treatment arm, combination of smoking status and prior multi-drug regimen (with 4 levels: Yes/Yes, Yes/No, No/Yes, and No/No) as fixed factors, and the Baseline 6MWD as a covariate will also be performed for the PP population. The between-treatment difference in LS mean change from baseline to Month 6, the corresponding 95% CI for the true between-treatment difference, and the p-value will be presented. Similarly, another supportive ANCOVA analysis of the change from baseline to Month 6 in 6MWD will be performed by using last observation carried forward method (i.e., missing 6MWD value at Month 6 will be replaced by last non-missing post-baseline value) for ITT.

As exploratory analyses, for the ITT population, the changes from baseline to Month 8, EOT and 3 months off treatment in 6MWD will be analyzed using a similar MMRM analysis with an unstructured covariance matrix. Each analysis will use the data over all post-baseline visits up to that time point. Also, these analyses will consider the following covariance structures for the within-subject observations: unstructured, heterogeneous, first-order autoregressive, Toeplitz, and compound symmetry. The between-treatment differences in LS mean changes from baseline to Month 8, EOT, and 3 months off treatment, the corresponding 95% CIs for the true between-treatment differences, and the p-values from this analysis will be presented from the corresponding analysis.

As an exploratory analysis of 6MWD, ANCOVA analysis of the change from baseline to Month 6 within the treatment arm of LAI plus a multi-drug regimen will be performed to compare converters with non-converters for the ITT population. The ANCOVA model will include change from baseline to Month 6 in 6MWD as response variable, converters vs non-converters as a factor, combination of smoking status and prior multi-drug regimen (with 4 levels: Yes/Yes, Yes/No, No/Yes, and No/No) as a fixed factor and baseline 6MWD as covariate. A similar analysis will be performed within multi-drug regimen alone. The difference in LS mean change from baseline to Month 6 between

converters and non-converters, the corresponding 95% CI for the true difference, and the p-value will be presented for each analysis.

11.3: Time to Culture Conversion:

Time to culture conversion for subjects achieving culture conversion is defined in Section 10.1. Recall that, for subjects not achieving culture conversion, time to culture conversion is censored at the subjects last day on the study or on the day of their Month 4 visit (whichever is earlier). Analyses of time to culture conversion will be performed for ITT population.

Kaplan-Meier estimates of the time-to-conversion curves will be produced for the two treatment arms. Median time to conversion together with the 25th and 75th percentiles and their associated 95% CIs will be presented by treatment arm as well as the p-value for the log rank test. 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 and the log rank test.

```
PROC LIFETEST DATA = INPUT_DATA METHOD = KM;
    TIME DAYS * CENSOR (1);
    STRATA TRT / TEST = LOGRANK;
```

DAYS is the number of days 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 whether censoring occurred (CENSOR = 1).

Time to conversion will also be analyzed using a Cox regression model to estimate the treatment effect (hazard ratio) adjusted for the two binary stratification factors (smoking status and prior multi-drug regimen). The hazard ratio, along with its 95% CI and p-value will be presented.

The following lines provide sample SAS code for the Cox regression model analysis.

```
PROC PHREG DATA = INPUT_DATA;
CLASS BSPMS TRT (ref= ‘Multi-Drug Regimen');
MODEL DAYS * CENSOR (1) = BSPMS TRT/ RL;
```

Again, DAYS is the number of days 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 whether censoring occurred (CENSOR = 1). BSPMS is the combination of smoking status and prior multi-drug regimen.

11.4 Culture conversion with durability and sustainability:

The proportion of subjects achieving culture conversion with durability (i.e. durability at 3 months off treatment, durability at EOS) and the proportion of subjects achieving culture conversion with sustainability will be analyzed for the ITT population using the Cochran-Mantel-Haenszel test (stratified by smoking status and prior multi-drug regimen) that was used for the primary endpoint analysis. As a supportive analysis, the proportion of subjects achieving culture conversion with durability at 3 months off treatment will also be evaluated for PP population.

11.5 SGRQ analysis:

The SGRQ domain scores and total score will be analyzed using an MMRM analysis of the change from baseline in the scores at Month 3 and Month 6 that is the same as that used for change from baseline in the 6MWD at Month 6 (i.e., MMRM will include data for Months 4 and 6). The between-treatment difference in LS mean change from baseline to Month 6, the corresponding 95% CI for the true between-treatment difference, and the p-value will be presented. SGRQ analyses will be performed for ITT population.

11.6 EQ-5D-3L:

The EQ-5D-3L index scores and VAS scores will be analyzed (separately) using an MMRM analysis of the change from baseline in the scores at all post-baseline visits that is the same as that used for change from baseline in the 6MWD at EOT (i.e., MMRM will include all post-baseline visits up to EOT). The between-treatment difference in LS mean change from baseline to EOT, the corresponding 95% CI for the true between-treatment difference, and the p-value will be presented. EQ-5D-3L analyses will be performed for ITT population.

11.7 New strains of MAC:

New strains of MAC in subjects that achieved culture conversion that are identified at post baseline will be recorded in source data. Incidence of new MAC strains will be summarized by treatment arm. New strains of MAC analyses will be performed for ITT population.

11.8 CT scan:

The incidences of different categories of findings from the CT scan at EOT will be summarized by treatment arm. If a CT scan is not performed at EOT for any subject, then prior CT scan will be used in the analysis. CT scan analyses will be performed for ITT population.

11.9 Mortality analyses:

Time to death will be summarised using the Kaplan-Meier estimates. Median survival time together with the 25th and 75th percentiles and associated 95% of confidence interval (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 live subject. Kaplan-Meier curve for time to death will also be provided. The treatment variable is binary and will be coded 1 if the subject was randomised to receive LAI administered QD plus a multi-drug regimen and 0 if the subject was randomised to receive a multi-drug regimen alone. The treatment effect (hazard ratio) will be estimated using the Cox proportional hazards regression model accounting for the two binary stratification factors (i.e., smoking status, prior multi-drug regimen) and age as a covariate. The comparison will be tested at two-sided alpha=0.05. Hazard ratio with confidence limits and p-value will be provided. In the event that there are not enough events (deaths) to fit Cox proportional hazards models, summary tables only will be provided.

11.10 Body Mass Index (BMI):

An ANCOVA analysis of the change from Baseline to Month 6 in BMI with treatment arm and combination of smoking status and prior multi-drug regimen (with 4 levels: Yes/Yes, Yes/No, No/Yes, and No/No) as a fixed factor, and the Baseline BMI as a covariate will also be performed for the ITT population. The between-treatment difference in LS mean change from baseline to Month 6, the corresponding 95% CI for the true between-treatment difference, and the p-value will be presented.

12.PHARMACOKINETIC ANALYSES

PK analyses are beyond the scope of this SAP and PK results will be reported separately.

13. SAFETY ANALYSES

All safety analyses will be based on the Safety population.

13.1 Extent of Exposure and Compliance

Study drug exposure will be summarized for each treatment 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 overall treatment period. Duration of treatment is defined as the difference between last dose date and the first dose date.

Since the subjects of multi-drug regimen alone arm may not be tracked with respect to drug accountability, compliance may be calculated only for LAI subjects. Compliance will be calculated by two periods: compliance from baseline to Month 6 and compliance from baseline to EOT. Study drug compliance will be calculated as follows:

- Compliance [%] = (Actual number of vial used)/(Prescribed number of vial to be used) ×100%
- Prescribed number of vials to be used = Number of days study medication to be taken (based on the duration of treatment). Prescribed number of vial per visit (month) is 30. As subjects will interrupt treatment for 2 days prior to their scheduled Monthly visits, the compliance calculation will be based on 28 prescribed vials. At all visits except for visit (month) 10 and 12, prescribed number of doses to be taken is the last dose date at that visit (month) minus the first dose date at that visit (month) minus 2 plus 1. At visit (month) 10 and 12, prescribed number of doses to be taken is the last dose date at that visit (month) minus the first dose date at that visit (month) plus 1.
- Actual number of vial used is collected in eCRF.

Study drug compliance will be summarized by treatment arm 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

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. 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 treatment arm. 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 unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of most common (≧5%) TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs adjusted for exposure by MedDRA system organ class and preferred term. Subject-years incidence will be computed as the number of unique subjects who experienced the event during the study divided by the sum of the number of years each subject is in the study. 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 highest severity (i.e., Mild, Moderate and Severe). At each level of subject summarization a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary.
- 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 according to 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 according to 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 according to 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 summarised using Kaplan-Meier 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. Kaplan-Meier curve for time to first SAE will also be provided. In the event that there are not enough events (SAE), summary table only 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. Descriptive statistics at baseline and change from baseline is limited to continuous data.

Shift tables (i.e., 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 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 percentages of subjects with laboratory values exceeding clinically relevant thresholds as defined by CTCAE Version 4.03 will be summarized.

Clinical laboratory results will be provided in subject listings.

13.4 Vital Signs

Vital signs (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.

13.5 Physical Examination

Physical examination results will be included in data listings only.

13.6 Electrocardiogram

Electrocardiogram (ECG) results will be included in data listings only.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The protocol states that subjects in the PP population must have met the inclusion/exclusion criteria. The entry criteria, in total, were intended to help decide who should enter the trial, not to determine who should be included in statistical analyses. Only subjects who fail to meet major entry criteria will be excluded from the PP population, and these determinations will be made prior to data base lock.

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 (e.g., 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 (RTF) file.

Tables

- Formal organization of tabulations may be changed during programming if appropriate, e.g., 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 (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 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) (e.g., ADaM).

Listings

- Formal organization of the listing may be changed during programming if appropriate, e.g., 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, geographic region, subject number, visit, and date/time as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 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 (i.e., 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 (i.e., 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:

<u>Start Dates</u>

- 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 (e.g., ??-???-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 (e.g., ??-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 (e.g., ??-???-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. http://www.euroqol.org/about-eq-5d/publications/user-guide.html