

# **Liposomal Amikacin for Inhalation (LAI)**

NCT02628600

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

Phase 3

**Protocol Amendment #3.1**

**Version Date: 25 May 2017**

**EudraCT No.: 2015-003170-33**

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(Hereinafter called Insmed)

**Drug name**

Liposomal Amikacin for Inhalation (LAI)

**Protocol Title**

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 Number**

INS-312

EudraCT Number

2015-003170-33

**Name of Approver**

[REDACTED]

**Title of Approver**

[REDACTED]

Signature of Approver

[REDACTED]

Date: 25 May 2017

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Approve



26-May-2017 18:19:31 GMT+0000

**SIGNATURE PAGE FOR THE INVESTIGATOR****Protocol Number**

INS-312

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/EC responsible for this study.

I agree that the Sponsor, Insmad Incorporated, or its representatives shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name of Insmad Incorporated, or study drug code in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol, without the prior written consent of Insmad Incorporated.

**Name of Approver**

Type or print name of signer.

Signature of Approver \_\_\_\_\_

Date: mm/dd/yyyy

06/15/2017

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## SUMMARY OF CHANGES

Section	Change	Rationale
Multiple	Style, format and typographical edits	Corrected any spelling errors, removed/added punctuation marks and spaces, used abbreviations consistently, and deleted/revised/added phrases or hyperlinks to ensure stylistic consistency throughout the document.
Important Contacts	Updated Insmmed personnel	Change in Insmmed personnel required an update to the contact information.
Synopsis 9.4	The INS-312 study will comprise of two analyses. The first analyses will assess the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6; the time to culture conversion (defined by the date of the first of at least 3 consecutive monthly culture specimens that are MAC negative); and the mean change from Baseline in the 6MWT distance by Month 6 of the study, as well as the safety and tolerability of LAI. The latter analyses will be the final analyses at the completion of the study and will include all other endpoints.	The first analyses for Study INS-312 are based on their alignment with the first analyses in Study INS-212. Because of the recruitment period for Study INS-212 being longer than anticipated, the Sponsor believes that there will be numerous subjects in Study INS-312 reaching Month 6 by the data cut-off date (for the NDA submission under sub-part H). The data obtained for culture conversion by Month 6 from Study INS-312 will be able to provide support for the first analyses from Study INS-212, which will be incorporated into the integrated summary of efficacy (ISE) module. The latter analyses will be conducted at the completion of the study and will incorporate all other endpoints. Therefore, protocol INS-312 is being amended to allow for these analyses.

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## STUDY SYNOPSIS

<b>Study Title</b>	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 <i>Mycobacterium avium</i> complex (MAC) That are Refractory to Treatment
<b>Name of Test Drug/ Investigational Product</b>	Liposomal Amikacin for Inhalation (LAI)
<b>Active Pharmaceutical Ingredient</b>	Amikacin sulfate
<b>Objectives</b>	<p><b>Primary Objective</b></p> <p>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</p> <p><b>Secondary Objectives</b></p> <ol style="list-style-type: none"> <li>1. To evaluate the number of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 12/EOT (end of treatment)</li> <li>2. To evaluate the number of subjects achieving culture conversion by Month 6</li> <li>3. To evaluate the time to culture conversion</li> <li>4. To evaluate the change in the six-minute walk test (6MWT) distance at Month 6 and Month 12/EOT</li> </ol> <p><b>Exploratory Objectives</b></p> <ol style="list-style-type: none"> <li>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 II (Activities of Daily Living) at Month 6 and Month 12/EOT</li> <li>2. To assess the change from Baseline in the EQ-5D-3L questionnaire subject-reported health outcomes at Month 6 and Month 12/EOT</li> </ol>
<b>Study Description</b>	This open-label safety extension study will assess safety and tolerability of once daily dosing of 590 mg LAI added to a multi-drug regimen in subjects with NTM lung infections due to <i>Mycobacterium avium</i> complex (MAC) who are refractory to therapy. Eligible subjects will have successfully completed their Month 6 visit in the INS-212 study and confirmed to have not achieved the INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures) or have had a relapse or recurrence (agar positive or more than 2

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	<p>consecutive broth positive results after culture conversion has occurred) by Month 6; eligible subjects would subsequently also have completed their EOT visit in the INS-212 study.</p> <p>Sputum samples collected up to and including Month 6 in the INS-212 study will be used to determine eligibility of the subject. All subjects will continue the multi-drug anti-mycobacterial regimen that they were receiving (either alone or plus 590 mg LAI) during the INS-212 study and will receive LAI 590 mg QD for 12 months in INS-312.</p> <p><b>Study Rationale</b></p> <p>Treatment guidelines for patients with MAC lung infection in the published ATS/Infectious Diseases Society of America (IDSA) consensus document were based primarily on small uncontrolled or non-comparative studies in patients with predominantly severe or refractory MAC disease [Griffith et al, 2007].</p> <p>Overall, there remains a lack of sufficiently powered, prospective clinical trials aimed at the treatment of pulmonary MAC infection. Many of the drugs used in the prolonged, recommended multi-drug regimens are poorly tolerated [Ballarino, 2009]. It is clear from these single-site studies that there is an unmet need for more effective, less-toxic therapeutic options.</p> <p>Study TR02-112 was a randomized double-blind placebo controlled study that dosed 89 subjects with LAI or placebo added to a background multi-drug regimen. At Day 84, 25.0% of subjects with add-on LAI had a negative sputum culture compared to 6.7% of subjects with add-on placebo. This is an important result for this population as subjects were refractory to therapy for a minimum of 6 months to more than 2 years prior to enrollment.</p> <p>The ongoing INS-212 study has been designed to evaluate whether the signal identified in TR02-112 is further confirmed in a longer duration of LAI treatment in subjects with NTM MAC lung infections who are refractory to a multi-drug regimen for at least 6 months, by assessing culture conversion and durability at 3 months and 12 months off treatment.</p> <p>Study INS-312 is an open-label safety extension to the INS-212 study that will further evaluate the safety and tolerability of once daily dosing of 590 mg LAI added to a multi-drug regimen in subjects with MAC lung infections that are refractory to therapy. Eligible subjects are those who have successfully completed the Month 6 study visit in INS-212 and confirmed to have not achieved culture conversion (as defined in INS-212) or have had a relapse or recurrence after culture conversion has occurred by Month 6. These subjects will then be required to have completed their EOT visit in INS-212.</p> <p><b>Design</b></p> <p>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</p>
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	<p>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 monthly 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 cultures in INS-212. The scheduled Month 8 visit will become the EOT visit. Subjects will be asked to provide written informed consent for INS-312 and will enroll directly from the INS-212 study at their EOT visit after having met all eligibility criteria for INS-312.</p> <p>Eligible and 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.</p> <p>Expectorated sputum (spontaneous or induced [e.g., with nebulized hypertonic saline solution as needed]) collected at the INS-212 EOT study visit will be used as the Baseline (Day 1) sputum for the INS-312 study. It is recommended to collect at least 2 expectorated sputum specimens from subjects by every scheduled visit during the treatment phase. Subjects must interrupt LAI administration for 2 days prior to all scheduled study visits where a sputum sample will be obtained. If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable.</p> <p>All subjects will have routine visits at Day 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12/EOT. At these visits, vital signs, pulse oximetry, and urine pregnancy test (if woman of child bearing potential) will be performed. Safety laboratory assessments (chemistry, hematology, and urinalysis) and a healthcare resource utilization questionnaire will be conducted at Day 1, Months 1, 3, 6, 9, and 12/EOT. Physical examination and body weight measurements 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 (Day 1) measurement for the INS-312 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.</p> <p>Home Healthcare visits may be available at Months 2, 4, 5, 7, 8, 10, and 11 for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits.</p> <p>All subjects will return 1 month after EOT for an off-LAI treatment follow-up visit (EOS); this includes subjects that early terminated the study, as both the EOT and EOS visits will need to occur. At this visit, a</p>
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	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.
<b>Study Duration</b>	This study will begin once a subject has met all inclusion and none of the exclusion criteria; the subject will receive treatment with LAI in the study for 12 months (excluding observational follow-up).  Subjects may remain in the study for up to a total of 13 months (12 months on treatment plus 1 month off-LAI treatment for safety follow-up). Subjects will enroll directly from the INS-212 study at their EOT visit.
<b>Study Population</b>	The study is designed to screen only those subjects who were randomized in the INS-212 study. It is expected that approximately 200 subjects will be eligible for and enroll in this study. All subjects enrolled will be given LAI 590 mg QD plus their multi-drug regimen for 12 months. This study is planned to be conducted at approximately 150 sites in North America, Europe, and Asia-Pacific.
<b>Inclusion Criteria</b>	Subjects are eligible to participate in the study if they meet all the following inclusion criteria: <ol style="list-style-type: none"> <li>1. have successfully completed the Month 6 and EOT visits in INS-212</li> <li>2. have not achieved the INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 in INS-212 OR have experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred) by Month 6 in INS-212</li> <li>3. have demonstrated compliance with treatment regimen in INS-212, including LAI, if applicable</li> <li>4. willing to adhere to multi-drug treatment regimen during the study</li> <li>5. female of child bearing potential agrees to practice an acceptable method of birth control (e.g., true abstinence [refraining from heterosexual intercourse during the entire study], hormonal or barrier methods, partner sterilization, or intrauterine device [IUD]) while participating in the trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.</li> <li>6. the subject will provide written informed consent</li> <li>7. willing to have serum and sputum specimens stored</li> </ol>

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	8. able to comply with study drug use, study visits, and study procedures as determined by the Investigator
<b>Exclusion Criteria</b>	<p>Subjects are not eligible to participate in the study if they meet any of the following criteria:</p> <ol style="list-style-type: none"> <li>1. achieved culture conversion without relapse or recurrence in the INS-212 study by Month 6</li> <li>2. early discontinuation (prior to Month 6 study visit) from INS-212</li> <li>3. met any of the exclusion criteria of the INS-212 study, except for the following: <ol style="list-style-type: none"> <li>a. unable to perform the 6MWT</li> <li>b. prior exposure to LAI (including clinical study)</li> <li>c. in the opinion of the Investigator, patients who are not expected to survive the duration of the study</li> <li>d. active allergic bronchopulmonary mycosis or any other condition requiring chronic systemic corticosteroids at a dose greater than the equivalent of 10 mg/day of prednisone</li> <li>e. initiation of chronic therapy (e.g., high dose ibuprofen, inhaled anti-inflammatory agents including steroids, low dose maintenance steroids, rhDNase)</li> </ol> </li> <li>4. positive pregnancy test or lactation. All women of child bearing potential will be tested. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.</li> <li>5. significant (as determined by the Investigator) hearing loss, vestibular dysfunction, or neuromuscular weakness where the potential risk of aminoglycoside toxicity outweighs the potential benefit</li> <li>6. aspartate aminotransferase or alanine aminotransferase <math>\geq 3</math> times the upper limit of normal (ULN) and/or total bilirubin <math>\geq 2</math> times the ULN at their Month 6 study visit in INS-212</li> <li>7. absolute neutrophil count <math>\leq 500/\mu\text{L}</math> at their Month 6 study visit in INS-212</li> <li>8. serum creatinine <math>&gt;2</math> times ULN at their Month 6 study visit in INS-212</li> <li>9. current alcohol, medication abuse, or illicit drug abuse</li> <li>10. any condition that, in the opinion of the Investigator, interferes with ability to safely complete the study or adhere to study requirements.</li> </ol>

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	11. diagnosis of myasthenia gravis
<b>Study Withdrawal Criteria</b>	<p>A subject may be withdrawn from the study for any of the following reasons:</p> <ol style="list-style-type: none"> <li>1. the event of the subject's death</li> <li>2. the subject experiences an adverse event (AE) and the Investigator or the subject determines that withdrawal from the study is appropriate</li> <li>3. a major protocol deviation that interferes with the integrity of the study data for this subject</li> <li>4. the subject withdraws consent to participate in the study</li> <li>5. the site is unable to contact the subject after all reasonable efforts have been exhausted (Lost to Follow-Up)</li> <li>6. the subjects meet the following criteria established by Hy's law: alanine aminotransferase or aspartate aminotransferase <math>\geq 3</math> ULN AND total bilirubin <math>&gt; 2</math> ULN.</li> <li>7. the subject becomes pregnant</li> <li>8. any condition that, in the judgment of the Investigator, would compromise the ability of the subject to comply with the study protocol or complete the study (physician decision)</li> <li>9. the subject discontinues study drug permanently</li> </ol>
<b>Study Drug Administration</b>	<p>LAI will be supplied by Insmmed Incorporated in clear glass 10 mL vials for nebulization for a delivered dose of 590 mg. The study drug will be administered via inhalation using the PARI Pharma GmbH eFlow<sup>®</sup> nebulizer (eFlow<sup>®</sup> nebulizer), a small machine that delivers medication in the form of a mist inhaled into the lungs, which is approved by the European Medicines Agency for use in the European Union (elsewhere it is an investigational medical device that is not yet commercially approved).</p> <p>Study drug will be administered QD. Subjects who develop bronchospasm may be pre-treated with a bronchodilator before study drug administration. Subjects who were pre-treated with a bronchodilator in the INS-212 study should continue to be pre-treated in the INS-312 study.</p>
<b>Methodology and Study Procedures</b>	See <a href="#">Table 3-1</a> Schedule of Events
<b>Study Endpoints</b>	<p><b>PRIMARY ENDPOINT - SAFETY</b></p> <p>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</p>

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	<p>measurements. The primary endpoint will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).</p> <p><b>SECONDARY ENDPOINTS - EFFICACY</b></p> <p>The secondary endpoints will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).</p> <ol style="list-style-type: none"> <li>1. Proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures without relapse or recurrence) by Month 12/EOT</li> <li>2. Proportion of subjects achieving culture conversion by Month 6</li> <li>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.</li> <li>4. The mean change from Baseline in 6MWT distance at Month 6 and Month 12/EOT</li> </ol> <p><b>EXPLORATORY ENDPOINTS - EFFICACY</b></p> <p>The exploratory endpoints will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).</p> <ol style="list-style-type: none"> <li>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)</li> <li>2. The mean change from Baseline at Month 6 and Month 12/EOT in the EQ-5D-3L</li> <li>3. Radiological changes in CT scan at EOT, within a sub-set of subjects</li> </ol>
<b>Efficacy Variables</b>	MAC identified in sputum specimens cultured in agar and broth, 6MWT results, and SGRQ and EQ-5D-3L scores
<b>Safety Variables</b>	The frequency of TEAEs, TEAEs leading to withdrawal from study, treatment-emergent SAEs, AEs of special interest, clinically significant abnormal laboratory test results, audiology test results, and vital signs measurements
<b>Statistical Methods</b>	<b>Sample Size Determination</b>

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	<p>There is no sample size determination as this study follows the INS-212 study; eligible subjects who consent after Month 6 and complete the EOT visit of the INS-212 study will determine the sample size of this study.</p> <p><b>Statistical Methodology</b></p> <p>The INS-312 study will comprise of two analyses. The first analyses will assess the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6; the time to culture conversion (defined by the date of the first of at least 3 consecutive monthly culture specimens that are MAC negative); and the mean change from Baseline in the 6MWT distance by Month 6 of the study, as well as the safety and tolerability of LAI. The latter analyses will be the final analyses at the completion of the study and will include all other endpoints.</p> <p>The safety endpoints are the frequency of TEAEs, TEAEs leading to withdrawal from study, treatment-emergent SAEs, AEs of special interest, clinically significant abnormal laboratory test results, and vital signs measurements. The safety analysis will be performed for the safety population.</p> <p>All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). AEs starting between first study drug administration in INS-312 and 1 month after last study drug administration will be regarded as treatment emergent.</p> <p>The number and percentage of subjects with TEAEs, TEAEs leading to withdrawal from study, and treatment-emergent SAEs will be tabulated by System Organ Class and Preferred Term overall and by the treatment arm in INS-212. Furthermore, the incidence of TEAEs by worst grade of severity will also be tabulated by System Organ Class and Preferred Term overall and by the treatment arm in INS-212.</p> <p>AEs that are not treatment-emergent will be listed.</p> <p>For all other safety data (vital sign measurements, clinical laboratory values, audiology test results, and physical examination findings) 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 arm in INS-212 using descriptive statistics.</p> <p>The proportion of subjects achieving negative sputum culture conversion by Month 12/EOT and Month 6 will be summarized overall and by previous treatment arm in INS-212. Kaplan Meier estimates for the distribution of time to culture conversion will be constructed for the treatment arms in INS-212. The changes in 6MWT distance, SGRQ, SGRQ-Part II, EQ-5D-3L, and subject-reported symptoms of NTM will be summarized across all the study visits overall and by the previous treatment arm in INS-212 for the safety population.</p>
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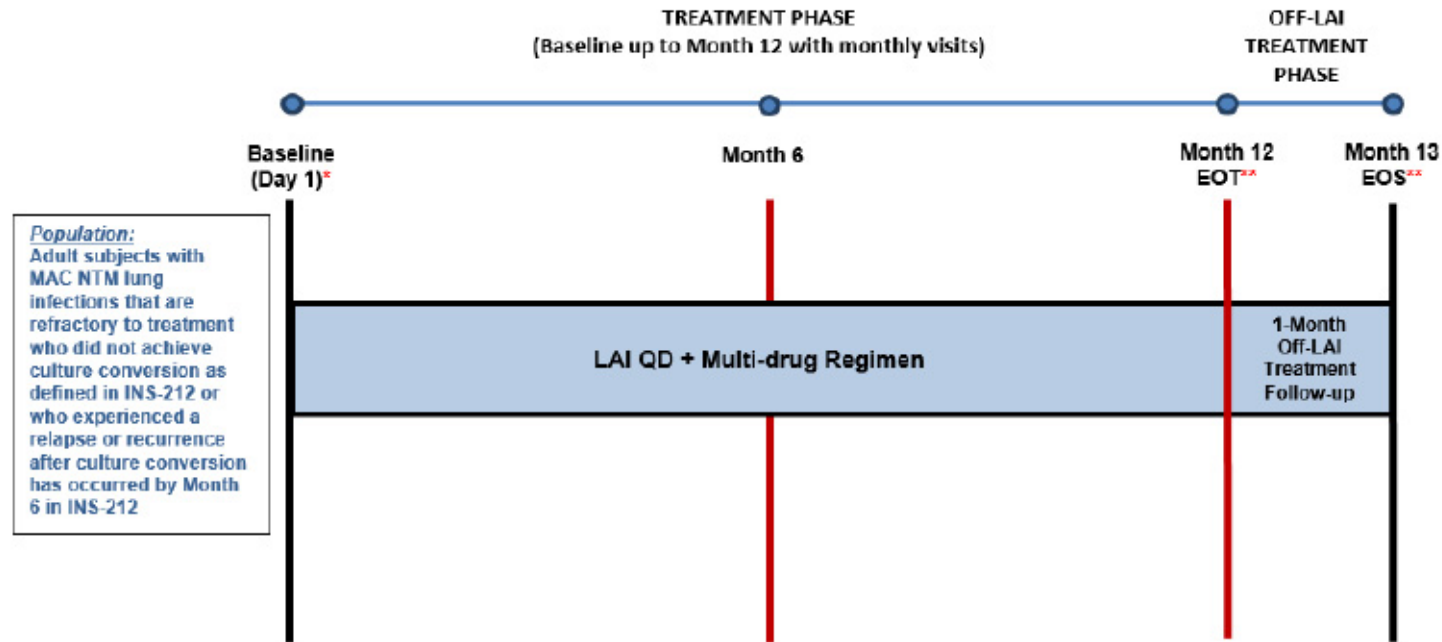
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	CT scan data will be summarized overall by previous treatment arm in INS-212 for both subjects in the CT scan sub-study and subjects in the Japan specific CT scan sub-study.
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\* Baseline (Day 1) 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

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Term</b>
6MWT	Six-minute walk test
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
BR	Bronchiectasis
CF	Cystic Fibrosis
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DPPC	Dipalmitoylphosphatidylcholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EQ-5D-3L	Formerly EuroQol 5D, a generic health-status classification instrument
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration of the United States of America
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
EC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine Device

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Abbreviation	Term
IV	Intravenous
LAI	Liposomal Amikacin for Inhalation
MAC	<i>Mycobacterium avium</i> complex
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
NTM	Nontuberculous Mycobacteria
<i>Pa</i>	<i>Pseudomonas aeruginosa</i>
PI	Principal Investigator
PP	Per-Protocol
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St. George's Respiratory Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TOBI	Tobramycin for Inhalation
ULN	Upper Limit of Normal
w:w	Weight to Weight

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## 1 INTRODUCTION

### 1.1 BACKGROUND

#### 1.1.1 Nontuberculous Mycobacterial Lung Infections

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment. The pulmonary infection caused by these organisms has features that overlap with tuberculosis, but disease definition can be more complex as recovery of a single isolate from the airway secretions does not necessarily indicate disease. In contrast to tuberculosis, there is no convincing evidence of person-to-person spread (Griffith, 2007; Olivier, 2003). It appears that the prevalence of human disease attributable to these organisms over the past 2 decades is increasing (Khan, 2007; Marras, 2007; Khan, 2008). Pulmonary disease due to NTM was traditionally reported as primarily upper lobe fibrocavitary disease occurring in male smokers with emphysema (Contreras, 1988). More recently, certain disease and demographic populations seem to be particularly susceptible to nodular bronchiectatic pulmonary disease with predominant infection of the anterior aspect of the mid-lung. In cystic fibrosis (CF), the prevalence of NTM in the lower airways is 13%, and increases with age (Olivier, 2003). Elderly, Caucasian women without apparent predisposing conditions have been reported with increasing frequency to have pulmonary disease associated with *Mycobacterium avium* complex (MAC), and one community pulmonary practice reported this to be a prominent cause of chronic cough with infiltrates (Prince, 1989).

*Mycobacterium avium* and MAC, a symbiotic infection of *M. avium* and *M. intracellulare*, are the predominant infective species in NTM pulmonary disease in US, Japan, European countries and elsewhere, followed by *M. abscessus* and *M. kansasii*. There is a perception that *M. abscessus* as a causative species is on the rise, which is a concern because these infections are especially difficult to treat (Leung, 2013; Olivier, 2003). In CF, the rates of NTM lung infection caused by *M. abscessus* often exceed those caused by MAC.

Signs and symptoms of NTM pulmonary infection are variable and nonspecific. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM lung infection.

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Evaluation is often complicated by the symptoms caused by co-existing lung diseases. These conditions include chronic obstructive airway disease (COPD) associated with smoking, bronchiectasis, previous mycobacterial diseases, CF, and pneumoconiosis (Wilson, 1997).

Current treatment of NTM lung infection is primarily with multi-drug regimens developed for the treatment of tuberculosis. This approach is not optimal, and the morbidity and mortality associated with NTM infection is significant. A study by Andrejak in Denmark demonstrated that mortality after 5 years in those who were infected per the American Thoracic Society /Infectious Diseases Society of America (ATS/IDSA) criteria was 40%. In this study, *M. xenopi* was associated with a particularly poor prognosis (Andrejak, 2010).

### 1.1.2 Liposomal Amikacin for Inhalation (LAI)

LAI is a sterile aqueous liposomal formulation for inhalation via nebulization. LAI is comprised of amikacin sulfate encapsulated in liposomes composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol; other inactive ingredients include sodium chloride, sodium hydroxide for pH adjustment and water for injection. LAI is supplied in a single use 10 mL vial to deliver 590 mg amikacin to the nebulizer. LAI is administered by inhalation via a PARI eFlow® nebulizer, a small machine that delivers medication in the form of a mist inhaled into the lungs, which is approved by the European Medicines Agency (EMA) for use in the European Union (elsewhere it is an investigational medical device that is not yet commercially approved).

### 1.1.3 Prior Clinical Experience

LAI is a novel formulation of amikacin that is encapsulated in liposomes comprised of DPPC and cholesterol (naturally occurring lipids in the lung) to allow for effective delivery in the lung, leading to high concentrations of the drug at the target sites of infection, with low systemic levels. Clinical studies to date have evaluated LAI in a total of 519 subjects, including 6 healthy subjects, 383 subjects with CF, 43 subjects with bronchiectasis (BR), and 89 subjects with NTM lung disease in Canada, Europe, and the United States. Early studies in the clinical development program established that LAI was effective in improving lung function in CF subjects with chronic *Pseudomonas aeruginosa* (*Pa*) lung infection. The pivotal phase 3 study that supports efficacy in the management of chronic *Pa* in subjects with CF is TR02-108 in which LAI was

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non-inferior to tobramycin for inhalation (TOBI). An open-label extension to TR02-108, the TR02-110 study, established a sustained effect of LAI in these subjects for up to 30 months. These data are supported by earlier studies assessing LAI against placebo for short cycles of treatment (TR02-105 and TR02-106) in which LAI demonstrated statistical superiority over placebo. All controlled comparator studies (TR02-105, 106, 108, and 110) established an additional benefit in quality of life measures for these subjects.

The program also included a study in subjects with NTM lung infection (TR02-112) that randomized and dosed 89 subjects with LAI or placebo added to a background multi-drug regimen. The primary endpoint evaluated mycobacterial load in sputum at the end of the double-blind period (Day 84) utilizing the semi-quantitative scale (SQS); there was no statistically significant difference between subjects dosed with LAI or placebo. The key secondary endpoint assessed sputum cultures and demonstrated that more subjects in the LAI arm achieved a negative sputum culture at Day 84 than subjects in the placebo arm. These results are presented in [Section 1.2 Rationale for the Study](#).

The results of clinical studies of LAI are summarized in the Investigator's Brochure (IB).

## 1.2 RATIONALE FOR THE STUDY

Treatment guidelines for patients with MAC lung infection in the published ATS/IDSA consensus document were based primarily on small uncontrolled or non-comparative studies in patients with predominantly severe or refractory MAC disease ([Griffith, 2007](#)).

Overall, there remains a lack of sufficiently powered, prospective clinical trials aimed at the treatment of pulmonary MAC infection. Many of the drugs used in the prolonged, recommended multi-drug regimens are poorly tolerated ([Ballarino, 2009](#)). It is clear from these single-site studies that there is an unmet need for more effective, less-toxic therapeutic options.

Amikacin solution for parenteral administration is an established drug that is effective against a variety of NTM. However, its use is limited by poor tissue penetration into lung tissue and the need to administer it intravenously (IV) in high enough doses that cause toxicity to hearing, balance, and kidney function. In the case of bacterial infections of the lung, the inhalation route of administration is advantageous over the IV route in that the aminoglycoside is delivered

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directly to the effect-site with neither significant systemic absorption nor the associated systemic toxicities. Disadvantages of aerosolized aminoglycoside solutions include rapid clearance from lung tissue, which necessitates frequent dosing (Geller, 2002) and the length of time required to inhale sufficient amounts of drug. Both factors place a high daily treatment burden on patients and may limit patient compliance. Thus, LAI was developed to overcome these limitations.

Lipid/liposome delivery systems like that used to deliver LAI in this study have been used to improve the therapeutic index of several injectable therapeutic agents. In a liposome drug delivery system, a bioactive agent entrapped in a liposome is administered to the patient. Alternatively, drugs can be combined with lipids to form nonencapsulated lipid drug complexes having therapeutic advantages. Therapeutic properties of several commercial products, such as anticancer compounds liposomal doxorubicin (Doxil<sup>®</sup>) and liposomal daunorubicin (Daunosome<sup>®</sup>) and the antifungal lipid complex of amphotericin B (Abelcet<sup>®</sup>, Ambisome<sup>®</sup>), have improved dramatically after encapsulation or complexing with a lipid. Although these commercial products are administered IV, inhaled Ambisome is being evaluated for prophylactic use.

Study TR02-112 was a randomized double-blind placebo controlled study that dosed 89 subjects with LAI or placebo added to a background multi-drug regimen. The primary endpoint evaluated mycobacterial load in sputum at the end of the double-blind period (Day 84) utilizing the semi-quantitative scale (SQS); there was no statistically significant difference between subjects dosed with LAI or placebo. At Day 84, 25.0% of subjects with add-on LAI had a negative sputum culture compared to 6.7% of subjects with add-on placebo. This is an important clinical result in this population as subjects were refractory to therapy for a minimum of 6 months to more than 2 years prior to enrollment. Furthermore, 12 subjects demonstrated sustained negative culture results with add-on LAI to the end of the open-label phase (Day 168) including the 28 days off LAI follow-up period.

The change in subject functional status was assessed using the 6-minute walk test and a statistically significant difference in favor of LAI (a mean increase from Baseline [Day 1] of 23.859 meters vs. a mean decrease of 25.032 meters in the LAI vs. placebo arms, respectively ( $p = 0.0134$ )).

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The ongoing INS-212 study will evaluate whether the signal identified in TR02-112 is further confirmed in a longer duration of LAI treatment in subjects with NTM MAC lung infections who are refractory to a multi-drug regimen for at least 6 months.

Study INS-312 is an open-label safety extension study to the INS-212 that will further evaluate the safety and tolerability of once daily dosing of 590 mg LAI plus a multi-drug regimen in subjects with NTM lung infections who are refractory to therapy. Eligible subjects will have successfully completed their Month 6 visit in INS-212 and confirmed to have not achieved the INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures), or have had a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred) by Month 6, as determined by their sputum culture results from Day 1 through Month 6; eligible subjects would subsequently have also completed their EOT visit in the INS-212 study.

In these patients who failed to respond to treatment, there are no recommended therapeutic alternatives. Modification or intensification of therapy may be done, but this strategy is not well supported in the literature and may risk patient tolerability of the medications (Griffith, 2012). An aminoglycoside such as amikacin or streptomycin is often added to the treatment regimen when the patient fails to respond to initial therapy. The addition of fluoroquinolones has also been tried, but there is little evidence to support the use of fluoroquinolones in the treatment of MAC lung disease. These patients will therefore continue their multi-drug antibiotic regimen, with add-on LAI as part of that treatment regimen. The inclusion of these patients into Study INS-312 would provide another opportunity for these patients to achieve sputum culture conversion through the addition of LAI onto their multi-drug antibiotic regimen.

### 1.3 RISK-BENEFIT ASSESSMENT

The safety of LAI has been evaluated in 13 studies, 11 of which are completed and 2 are ongoing. The 6 main safety studies (TR02-105, TR02-105 extension, TR02-106, TR02-108, TR02-110 and TR02-112) conducted in CF and NTM included a total of 434 unique treated subjects who received LAI at doses ranging from 70 mg QD to 590 mg QD. In all 6 of the main safety studies, most subjects were Caucasian and the majority were female.

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In each of the 6 main safety studies, most the subjects in all treatment arms experienced at least 1 treatment-emergent adverse event (TEAE), with most events related to the subjects' underlying diagnosis. Across the 6 main safety studies, the most common serious adverse event (SAE) in all groups was hospitalizations due to pulmonary exacerbation. Most SAEs were not considered by the Investigator to be treatment-related. In TR02-112, in the double-blind phase, SAEs were reported for a greater proportion of subjects in the LAI arm than in the placebo arm (18.2% versus 8.9%, respectively). The incidence of SAEs did not increase in the LAI arm after additional exposure to the study drug in the open-label phase of TR02-112 compared with the double-blind phase (14.3% vs. 18.2%, respectively).

In preclinical studies, treatment-related lung tumors were observed at the end of 2 years of dosing in 2 of 120 rats. The theoretical risk of lung tumors must be weighed against the potential benefits of LAI for patients, and will depend on several factors, including severity of disease, comorbidities and the availability of alternative treatments.

Additional details of clinical studies and potential AEs evidenced from preclinical studies are presented in the Investigator's Brochure (IB) [[LAI IB, 2016](#)].

## 2 STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the long-term safety and tolerability of LAI (590 mg) administered 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 SECONDARY OBJECTIVES

The secondary objectives are:

1. To evaluate the number of subjects achieving culture conversion (3 consecutive monthly 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.

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4. To evaluate the change in the six-minute walk test (6MWT) distance at Month 6 and Month 12/EOT

### 2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are:

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 II (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

## 3 INVESTIGATIONAL PLAN

### 3.1 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 monthly 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) by Month 6. The scheduled Month 8 visit will become the EOT visit. Subjects will be asked to provide written informed consent for INS-312 and will enroll directly from the INS-212 study at their EOT visit after having met all eligibility criteria for INS-312.

Subjects in INS-212 have either received 590 mg LAI plus a multi-drug regimen or multi-drug regimen alone. All subjects in this safety extension study will continue the multi-drug anti-mycobacterial regimen that they were receiving during the INS-212 study and will receive LAI 590 mg once daily for up to 12 months. The subjects will remain in the study for up to a total of 13 months (up to 12 months on-treatment plus 1 month off-LAI treatment for safety follow-up).

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Expectorated sputum (spontaneous or induced [e.g., with nebulized hypertonic saline solution as needed at the clinical site only]) collected at the INS-212 EOT study visit will be used as the Baseline (Day 1) sputum for this study. It is recommended to collect at least 2 expectorated sputum samples from subjects by every scheduled visit during the treatment phase. Subjects must interrupt LAI administration for 2 days prior to all scheduled study visits where a sputum sample will be obtained. 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 routine visits at Day 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12/EOT. At these visits, vital signs, pulse oximetry, and urine pregnancy test (if woman of child bearing potential) will be performed. Safety laboratory assessments (chemistry, hematology, and urinalysis) and a healthcare resource utilization questionnaire will be conducted at Day 1, Months 1, 3, 6, 9, and 12/EOT. Physical examination and body weight measurements 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 (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.

Home Healthcare visits may be available at Months 2, 4, 5, 7, 8, 10, and 11 for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits.

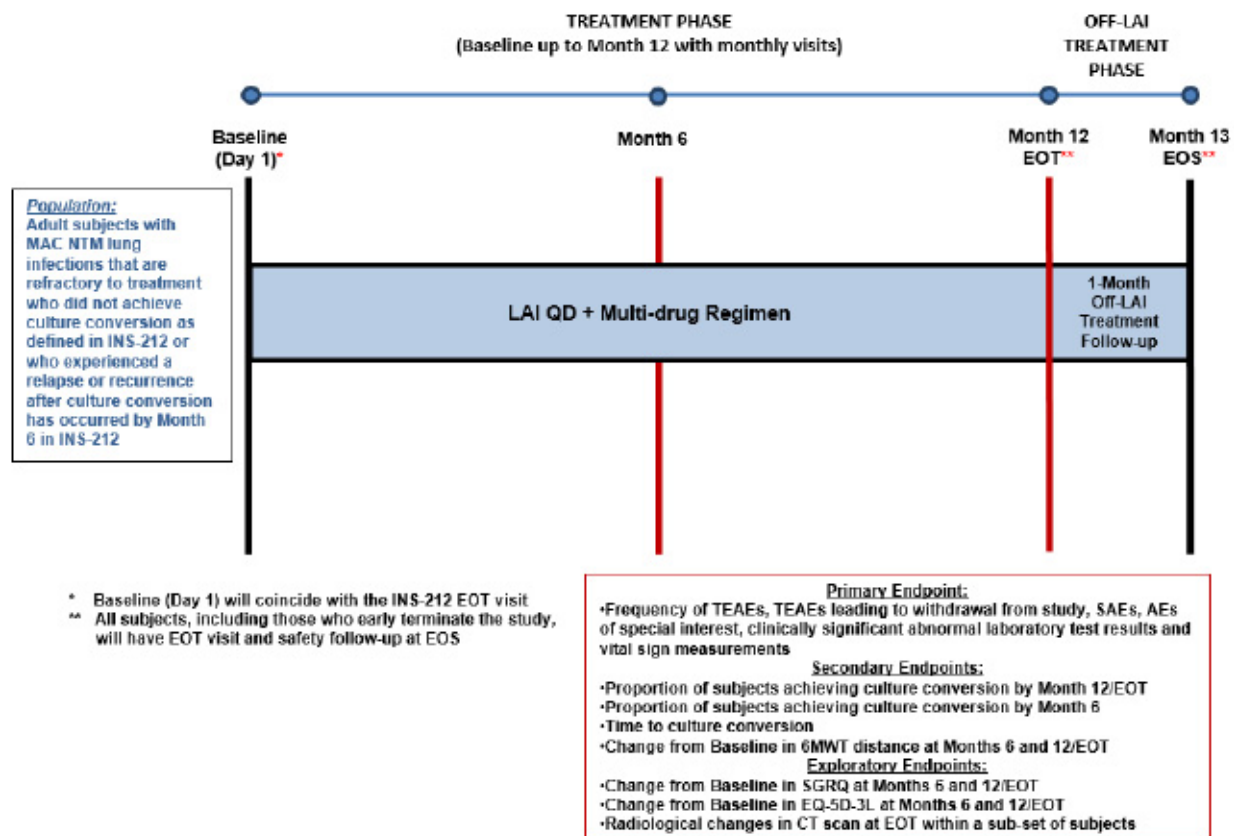
All subjects will return 1 month after their EOT to have an off-LAI treatment follow-up visit (EOS: End of Study) performed; this includes subjects who early terminate the study as both the EOT and EOS visits will need to occur. At this visit, a physical examination (including vital signs, pulse oximetry and weight), SGRQ, and EQ-5D-3L will be performed.

Unscheduled visits will occur as needed should subjects' symptoms worsen between visits.

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Figure 3-1 Study Design



### 3.2 PRIMARY ENDPOINT - SAFETY

The primary endpoint is the frequency of treatment emergent adverse events (TEAEs), TEAEs leading to withdrawal from study, treatment-emergent serious adverse events (SAEs), adverse events (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 (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).

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### 3.3 SECONDARY ENDPOINTS - EFFICACY

The secondary endpoints will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).

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 at Month 6 and Month 12/EOT

### 3.4 EXPLORATORY ENDPOINTS - EFFICACY

The exploratory endpoints will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).

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

### 3.5 SCHEDULE OF EVENTS

The schedule of events is presented in [Table 3-1](#). Detailed procedures and assessments performed at each scheduled study visit are presented in [Section 6](#).

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Table 3-1 Schedule of Events

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	Day 1	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)
Informed Consent <sup>b</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History <sup>c</sup>	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test <sup>d</sup>	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 <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6 minute walk test	X	-	-	-	-	-	X	-	-	-	-	-	X	-
Audiology test	X <sup>f</sup>	-	-	-	-	-	X	-	-	-	-	-	X	-
Concomitant medications <sup>g</sup>	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 <sup>h</sup>	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	-

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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	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 <sup>i</sup>	X	–	–	–	–	–	–	–	–	–	–	–	X	–
Sub-Study: CT scan of chest <sup>j</sup> (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 <sup>k</sup>	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.

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- <sup>a</sup> 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.
- <sup>b</sup> Subjects will be asked to provide written informed consent at their INS-212 EOT visit.
- <sup>c</sup> 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.
- <sup>d</sup> 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.
- <sup>e</sup> At visits where study drug is administered, vital signs and pulse oximetry will be performed before and after study drug administration.
- <sup>f</sup> The Baseline audiology examination must be performed on Day 1 before the administration of study drug.
- <sup>g</sup> 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.
- <sup>h</sup> 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.
- <sup>i</sup> 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.
- <sup>j</sup> 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.
- <sup>k</sup> Study drug will be dispensed to all subjects up to and including the Month 11 visit.

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## 3.6 DISCUSSION OF STUDY DESIGN

### 3.6.1 Number of Subjects

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

### 3.6.2 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 treatment with LAI 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.

### 3.6.3 Premature Termination of Study Site

For reasonable cause, an individual Investigator may terminate participation prematurely. The Sponsor may also decide to terminate the study prematurely. Written notification of the termination to each affected investigational site is required. Some conditions that may warrant termination include the following:

- discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- decision on the part of the Sponsor to suspend or discontinue development of the drug
- decision by a regulatory authority or the Sponsor to stop the study at any time, where applicable

In the event of study discontinuation, subjects will discontinue the study drug and it will be left up to the Investigators' medical judgment to determine if the subjects should continue their multi-drug regimen for treatment of their condition.

The Sponsor will notify the regulatory authorities in all countries where the study is being conducted regarding the reason for terminating the study.

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### 3.6.4 Assignment to Study Drug

Eligible subjects will receive LAI (590 mg) QD in addition to their multi-drug regimen.

### 3.6.5 Data Monitoring Committee

To ensure the safety of subjects enrolled in this study, a Data Monitoring Committee (DMC) will be implemented. This will be the same LAI DMC that is reviewing Study INS 212 and the compassionate use program. The LAI DMC will consist of experts outside of Insmmed and who are not involved in study conduct. The LAI DMC will provide a centralized review function independent of the Insmmed clinical team and all other individuals associated with the conduct of the study. The LAI DMC will consist of at least two physicians with pulmonary expertise who are not investigators in the study and a statistician who is experienced in the evaluation of safety data. Further details are available in the LAI DMC charter.

## 4 STUDY POPULATION

To be eligible for enrollment, subjects must meet all the following inclusion criteria and none of the following exclusion criteria.

### 4.1 INCLUSION CRITERIA

Subjects are eligible to participate in the study if they meet all the following inclusion criteria:

1. have successfully completed the Month 6 and EOT visits in INS-212
2. have not achieved the INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 in INS-212  
OR  
have experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred) by Month 6 in INS-212
3. have demonstrated compliance with treatment regimen in INS-212, including LAI, if applicable
4. willing to adhere to multi-drug treatment regimen during the study

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5. female of child bearing potential agrees to practice an acceptable method of birth control (e.g., true abstinence [refraining from heterosexual intercourse during the study], hormonal or barrier methods, partner sterilization, or intrauterine device [IUD]) while participating in the trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
6. the subject will provide written informed consent
7. willing to have serum and sputum specimens stored
8. able to comply with study drug use, study visits, and study procedures as determined by the Investigator

#### 4.2 EXCLUSION CRITERIA

Subjects are not eligible to participate in the study if they meet any of the following criteria:

1. achieved culture conversion without relapse or recurrence in the INS-212 study by Month 6
2. early discontinuation (prior to Month 6 study visit) from INS-212
3. met any of the exclusion criteria of the INS-212 study, except for the following:
  - a. unable to perform the 6MWT
  - b. prior exposure to LAI (including clinical study)
  - c. in the opinion of the Investigator, patients who are not expected to survive the duration of the study
  - d. active allergic bronchopulmonary mycosis or any other condition requiring chronic systemic corticosteroids at a dose greater than the equivalent of 10 mg/day of prednisone within 3 months before Baseline (Day 1)
  - e. initiation of chronic therapy (e.g., high dose ibuprofen, inhaled anti-inflammatory agents including steroids, low dose maintenance steroids, rhDNase) at Baseline (Day 1)

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4. positive pregnancy test or lactation. All women of child bearing potential will be tested. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
5. significant (as determined by the Investigator) hearing loss, vestibular dysfunction, or neuromuscular weakness where the potential risk of aminoglycoside toxicity outweighs the potential benefit
6. aspartate aminotransferase or alanine aminotransferase  $\geq 3$  times the upper limit of normal (ULN) and/or total bilirubin  $\geq 2$  times the ULN at their Month 6 study visit in INS-212
7. absolute neutrophil count  $\leq 500/\mu\text{L}$  at their Month 6 study visit in INS-212
8. serum creatinine  $>2$  times ULN at their Month 6 study visit in INS-212
9. current alcohol, medication abuse, or illicit drug abuse
10. any condition that, in the opinion of the Investigator, interferes with ability to safely complete the study or adhere to study requirements
11. diagnosis of myasthenia gravis

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### 4.3 REMOVAL OF SUBJECTS

A subject may be withdrawn from the study for any of the following reasons:

1. the event of the subject's death
2. the subject experiences an AE and the Investigator or the subject determines that withdrawal from the study is appropriate
3. a major protocol deviation that interferes with the integrity of the study data for this subject
4. the subject withdraws consent to participate in the study
5. the site is unable to contact the subject after all reasonable efforts have been exhausted (Lost to Follow-Up)
6. the subject meets the following criteria established by Hy's law: alanine aminotransferase or aspartate aminotransferase  $\geq 3$  ULN AND total bilirubin  $> 2$  ULN.
7. the subject becomes pregnant
8. any condition that, in the judgment of the Investigator, would compromise the ability of the subject to comply with the study protocol or complete the study (physician decision)
9. the subject discontinues study drug permanently

A subject may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator.

Subjects who discontinue the study prematurely should be assessed in accordance with the EOT and EOS visits in [Sections 6.3](#) and [6.4](#).

### 4.4 REPLACEMENT OF SUBJECTS

Subjects will not be replaced.

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## 5 STUDY TREATMENTS

### 5.1 INVESTIGATIONAL STUDY DRUG

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 (Table 5-1). The total lipid to drug ratio is 0.57 to 0.77 w:w (weight to weight).

**Table 5-1 Composition of Liposomal Amikacin Sulfate**

Ingredient	Quality Grade	Mg/mL
Amikacin base (amikacin sulfate)	EP/USP	70
Cholesterol	HP <sup>a</sup>	15.7
Dipalmitoylphosphatidylcholine (DPPC)	In-house	31.5
Sodium chloride	USP/EP/JP	12
Sodium hydroxide	USP/EP/JP	QS to adjust pH
Water for injection	USP/EP/JP	QS

Abbreviations: EP, European Pharmacopeia; HP, High Purity; JP, Japanese Pharmacopeia; NF, National Formulary; USP, United States Pharmacopeia.

<sup>a</sup> HP grade meets or exceeds all requirements for cholesterol USP/NF/EP.

### 5.2 REFERENCE STUDY DRUG

None

### 5.3 ADMINISTRATION OF STUDY DRUG

LAI is administered daily by inhaling drug product that has been aerosolized in a PARI eFlow<sup>®</sup> nebulizer over approximately 14 minutes. Study drug will be administered daily by the subject except for the two days immediately prior to a scheduled study visit when sputum is collected (refer to Section 7.2.2). On the day of the study visit, after sputum is collected, the study drug

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will be administered at the study site by study personnel. Written directions for preparing and administering the study drug will be provided to subjects.

Subjects who develop bronchospasm may be pre-treated with a bronchodilator before study drug administration. Subjects who were pre-treated with a bronchodilator in the INS-212 study should continue to be pre-treated in this study.

### **Dose Interruption**

If a subject experiences local respiratory events such as, but not limited to, dysphonia, oropharyngeal pain, and cough while taking LAI that may be distressing to the subject, short interruptions of LAI may be necessary and are permitted. As the frequency of these local respiratory events decreased with continued use in prior LAI studies, it is recommended that LAI is reintroduced after a short interruption of dosing when symptoms subside. Please contact the medical monitor to discuss.

## **5.4 SELECTION OF DOSES**

All subjects enrolled in this open-label safety extension study will receive 590 mg of LAI once daily plus multi-drug regimen for 12 months.

Subjects who cannot tolerate 590 mg of LAI QD will be discontinued from the study (except for short interruptions as discussed in [Section 5.3](#)); the dose of LAI will not be changed during the study.

## **5.5 SELECTION OF TIMING OF ADMINISTRATION**

Study drug may be administered QD around the same time each day, any time of day, without regard to food.

## **5.6 BLINDING**

None

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## 5.7 STUDY KIT

Subjects will receive kits containing vials of LAI, the handset/nebulizer, and controller.

## 5.8 DRUG SUPPLY

The active ingredient, amikacin sulfate, is manufactured in accordance with cGMPs by ACS DOBFAR S.p.A. The single dose vials of the drug supplies are provided as follows: each kit of study drug contains a 7-day supply (7 single-dose vials).

### 5.8.1 Packaging

LAI is provided as a unit dose consisting of a 10 mL Type I clear borosilicate glass vial with a 20-mm finish using a closure system consisting of a 20 mm bromobutyl stopper and a 20-mm aluminum flip-off tear-off combination seal.

### 5.8.2 Labeling

Vials of study drug will be labeled as shown in [APPENDIX 2](#).

### 5.8.3 Storage

At the site, LAI must be stored at 2°C to 8°C (36°F to 46°F) in a secured place with restricted access. Do not freeze.

LAI will be provided to the subjects in an insulated cooler bag with cold pack for transport and shall be kept in the refrigerator while at home.

### 5.8.4 Compliance and Drug Accountability

Drug accountability will be recorded at each study visit by count of study vials.

A subject will be considered non-compliant to study drug if treatment adherence is less than 80% or more than 120% unless instructed by the Investigator to interrupt dosing for safety reasons ([Section 5.3](#)).

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### 5.8.5 Dispensing of Study Drug

Study drug (LAI) will be shipped to the study site. Subjects will be dispensed four or more 7-vial cartons per dispensing visit based on the study visit schedule, to allow for daily dosing, including extra supply for potential study visit scheduling delays.

### 5.8.6 Disposition and Reconciliation of Study Drug

Drug accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug accountability records including shipment receipts, study subject doses, and transfers to other locations within the study site. All transactions will be recorded on a real-time basis.

The pharmacy will maintain detailed documentation of the number and identification of vials with copies of these documents to be provided to the Sponsor at the end of the study. All used and unused boxes of study drug will be maintained by the site until inventoried by the study monitor. Upon completion of the drug inventory by the study monitor, used and any unused vials will be disposed of in accordance with instructions provided to sites and per site destruction policies. Documentation of destruction should be provided to the Sponsor

Accountability of the PARI eFlow® nebulizer will be maintained and tracked at the site. Subjects must return the nebulizers to the study site at the end of treatment. Additional instructions for handling the disposal or return of the devices will be provided to the sites and per site destruction policies.

## 5.9 CONCOMITANT MEDICATIONS

Throughout the duration of the study, including the 1 month off-LAI phase (Visit 14), subjects should continue the same, multi-drug, anti-mycobacterial regimen as prescribed from the INS-212 study. The regimen should be based on the 2007 ATS/IDSA Guidelines or respective local guidelines. Changes to concurrent anti-mycobacterial regimen will be at the discretion of the Investigator.

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Where allowed, and if approved by IRB/EC, the Sponsor may provide reimbursement of the multi-drug anti-mycobacterial regimen for if the subject participates in the study and is adherent to all protocol requirements. These drugs may include, but are not limited to: azithromycin, clarithromycin, clofazimine, ethambutol, ethionamide, rifabutin, and rifampicin.

All medications used during the study must be entered the concomitant medications electronic Case Report Form (eCRF).

## 5.10 PRECAUTIONARY MEDICATIONS

Treatment with oral or intravenous (IV) antibiotics for acute pulmonary exacerbations or acute infection is allowed as determined by the Investigator; the reason for use must be documented in the eCRF.

Although systemic exposure to amikacin is low after LAI administration, precaution should be taken if subjects require the following systemic medications that may have possible interactions with amikacin: potent diuretics (such as ethacrynic acid and furosemide), beta lactam antibiotics (such as penicillins and cephalosporins), bisphosphonates, platinum compounds, and thiamine. (Table 5-2)

Bronchodilator therapy is allowed. Subjects who develop bronchospasm may be pre-treated with a bronchodilator before study drug administration.

**Table 5-2 List of Examples of Precautionary Medications**

Name of Drug, etc.	Clinical Symptoms/ Treatment	Mechanism/ Risk Factor(s)
Potentially nephrotoxic blood substitutes such as Dextran Hydroxyethyl starch, etc.	Since there is a risk that nephrotoxicity occurs or is aggravated, concomitant use should be avoided.  When nephrotoxicity occurs, discontinue drug and implement appropriate	The mechanism of action is not completely clear but there are reports that the combination leads to deposits of aminoglycoside antibiotics in blood and to vacuolization of the proximal tubular epithelium.

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	treatment such as renal dialysis, etc.	
Loop diuretics Ethacrynic acid Furosemide Azosemide, etc.	Since both drugs may cause or aggravate nephro- and ototoxicity, concomitant use should be avoided	The mechanism of action is not completely clear but there are reports that the combination leads to increased blood concentration and renal deposits of aminoglycoside antibiotics
Nephrotoxic and ototoxic drugs such as Vancomycin, Enviomycin, Platinum-containing anti-cancer drugs (cisplatin, carboplatin, nedaplatin), etc.	Since both drugs may cause or aggravate nephro- and ototoxicity, concomitant use should be avoided	Both drugs are nephrotoxic/ ototoxic but the mechanism of action of the interaction is not known.
Anesthetics Muscle relaxants Tubocurarine Pancuronium bromide Tolperisone Botulinum type A toxin products, etc.	Risk of respiratory suppression. If respiratory suppression occurs, administer choline esterase inhibitor or calcium preparation, etc. as appropriate.	Both drugs have a neuromuscular inhibitory effect. Concomitant use will aggravate this effect.
Nephrotoxic drugs Cyclosporine A Amphotericin B, etc.	Risk that renal impairment occurs or is aggravated	Both drugs are nephrotoxic but the mechanism of the interaction is not known.

## 5.11 DISCONTINUATION OF STUDY

1. The Investigator may discontinue a subject from the study in the interest of subject safety. The Investigator must identify specific AEs (laboratory abnormality, intercurrent illness,

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other medical condition or situation) that result in premature discontinuation of the study in the eCRF.

2. A subject with a major protocol deviation that interferes with the integrity of the study data for this subject may be discontinued from the study
3. A subject who withdraws consent will be discontinued. All attempts must be made to conduct an EOT and an EOS visit (Sections 6.3 and 6.4).
4. Subjects who meet the following criteria established by Hy's law will be discontinued from the study: alanine aminotransferase or aspartate aminotransferase  $\geq 3$  ULN AND total bilirubin  $> 2$  ULN.
5. Subjects who become pregnant will be discontinued from the study and followed until the pregnancy is concluded.
6. Participation in the study will be discontinued in all subjects if the study or the site is terminated.
7. The subject discontinues study drug permanently

The Investigator must contact the medical monitor immediately before discontinuing a subject from the study if possible, or no later than 1 business day after the event. When a subject is discontinued from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate eCRF page describing the reason for discontinuation. Procedures required for an early discontinuation visit (EOT) must be performed.

If a subject is withdrawn from the study treatment because of an AE, the subject should be followed and treated by the Investigator until the abnormal parameter or symptom is resolved or stabilized. It is up to the Investigator to determine and document that the AE is either resolved or that it has reached a stable state, after which no further follow-up is necessary.

If a subject fail to complete scheduled assessments in the study, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. "Lost to follow-up" should be marked only in an exceptional case when all documented attempts to reach the subject by the Investigator or other staff members were unsuccessful.

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## 6 STUDY PROCEDURES

### 6.1 BASELINE VISIT (DAY 1, VISIT 1)

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. Procedures or assessments that are not part of the INS-212 cannot be performed until the subject has provided informed consent as documented on the Informed Consent Form (ICF).

All the following will be performed (if not already done for the INS-212 EOT visit):

- obtain medical history (this includes all ongoing medical history conditions from the INS-212. Any chronic conditions that require medication must be listed in the medical history eCRF.)
- solicit concomitant medications (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 dose in INS-312) (see [Section 7.1.5](#))
- administer SGRQ (Part I and II) before study drug administration (see [Section 7.3.1](#))
- administer EQ-5D-3L before study drug administration (see [Section 7.3.2](#))
- administer audiology test before study drug administration (see [Section 7.1.6](#))
- administer 6MWT before study drug administration (see [Section 7.2.1](#))
- administer physical examination, including vital signs, pulse oximetry and weight (see [Section 7.1.4](#) and [Section 7.1.3](#))
- obtain chest CT scan if part of CT Scan Sub-Study, if not already done for the INS-212 EOT visit (see [Section 7.3.4](#), [APPENDIX 3](#), [APPENDIX 4](#))
- collect information on healthcare resource utilization (see [Section 7.3.3](#))
- assess AEs (see [Section 7.1.1](#)). All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. Any AE that has occurred and resolved

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before administration of study drug on Day 1 (Baseline) will be documented as an AE for study INS-212. AEs will be assessed before and after administration of study drug.

- collect at least 2 sputum specimens for microbiological assessment (1 sample from one of the 2 days prior to scheduled study visit, 1 sample pre-dose at study visit). If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable. (see [Section 7.2.2](#))
- collect blood and urine specimens for clinical chemistry, hematology, and urinalysis testing and, for women of child bearing potential, a urine pregnancy test (see [Section 7.1.2](#))
- collect blood (serum) specimen for biomarker assessment (CRP and IL-6) ([Section 7.1.2](#))
- dispense sputum collection containers
- administer study drug at the study site (see [Section 5.3](#))
- dispense study drug

## 6.2 VISITS AT MONTH 1 (VISIT 2) TO MONTH 11 (VISIT 12) DURING THE TREATMENT PHASE

All the following should be performed or obtained at Month 1 (Visit 2) to Month 11 (Visit 12), unless otherwise noted,  $\pm 3$  days of the scheduled visit. Home Healthcare visits may be available at Months 2, 4, 5, 7, 8, 10, and 11 for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits.

- administer vital signs and pulse oximetry before and reassess after study drug administration. (see [Section 7.1.3](#))
- solicit concomitant medications (see [Section 7.1.5](#))
- assess AEs (see [Section 7.1.1](#))

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- recommend to collect at least 2 sputum specimens for microbiological assessment (1 sample from one of the 2 days prior to scheduled study visit, 1 sample pre-dose at study visit). If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable. (see [Section 7.2.2](#))
- for women of child bearing potential, a urine pregnancy test (see [Section 7.1.2](#))
- administer study drug at the study site (see [Section 5.3](#))
- dispense study drug
- dispense sputum collection containers
- collect previously dispensed study drug vials from subject

At Month 1 (Visit 2), Month 3 (Visit 4), Month 6 (Visit 7), and Month 9 (Visit 10) only:

- administer physical examination and weight measurement ([Section 7.1.4](#))
- collect information on healthcare resource utilization (see [Section 7.3.3](#))
- collect blood and urine specimens for clinical chemistry, hematology, and urinalysis testing (see [Section 7.1.2](#))

At Month 6 (Visit 7) only:

- administer SGRQ (Part I and II) before study drug administration (see [Section 7.3.1](#))
- administer EQ-5D-3L before study drug administration (see [Section 7.3.2](#))
- administer audiology test (see [Section 7.1.6](#))
- administer 6MWT before study drug administration (see [Section 7.2.1](#))
- collect blood (serum) specimen for biomarker assessment (CRP and IL-6) ([Section 7.1.2](#))
- (Japan only) obtain chest CT scan (see [Section 7.3.4](#), [APPENDIX 4](#))

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### 6.3 END OF TREATMENT (MONTH 12, VISIT 13) DURING THE TREATMENT PHASE

All the following should be performed or obtained  $\pm 3$  days of the scheduled visit:

- administer SGRQ (Part I and II) (see [Section 7.3.1](#))
- administer EQ-5D-3L (see [Section 7.3.2](#))
- administer audiology test (see [Section 7.1.6](#))
- administer 6MWT (see [Section 7.2.1](#))
- administer physical examination, including vital signs, pulse oximetry and weight (see [Section 7.1.4](#) and [Section 7.1.3](#))
- obtain chest CT scan if part of CT Scan Sub-Study, and no less than 6 months have elapsed since the previous CT scan was performed (see [Section 7.3.4](#), [APPENDIX 3](#), [APPENDIX 4](#))
- collect information on healthcare resource utilization (see [Section 7.3.3](#))
- solicit concomitant medications (see [Section 7.1.5](#))
- assess AEs (see [Section 7.1.1](#))
- recommend to collect at least 2 sputum specimens for microbiological assessment (1 sample from one of the 2 days prior to scheduled study visit, 1 sample pre-dose at study visit). If a subject is unable to produce sputum spontaneously, one induced sputum specimen collected at the clinical site will be acceptable. (see [Section 7.2.2](#))
- collect blood and urine specimens for clinical chemistry, hematology, and urinalysis testing and, for women of child-bearing potential, a urine pregnancy test (see [Section 7.1.2](#))
- collect blood (serum) specimen for biomarker assessment (CRP and IL-6) ([Section 7.1.2](#))
- collect all dispensed study drug vials from subject

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## 6.4 END OF STUDY (UP TO MONTH 13, VISIT 14) DURING THE OFF-LAI TREATMENT PHASE

All the following should have performed or obtained  $\pm 3$  days of the scheduled visit:

- administer SGRQ (Part I and II) (see [Section 7.3.1](#))
- administer EQ-5D-3L (see [Section 7.3.2](#))
- administer physical examination, including vital signs, pulse oximetry and weight (see [Section 7.1.4](#) and [Section 7.1.3](#))
- solicit concomitant medications (see [Section 7.1.5](#))
- assess AEs (see [Section 7.1.1](#))

The EOS visit for all subjects, including those who prematurely discontinued the study, is scheduled to occur 1 month after the EOT visit.

## 7 STUDY VARIABLES AND METHODS OF ASSESSMENT

### 7.1 PRIMARY ENDPOINT VARIABLES

Please refer to [Section 9.6](#) for more details.

#### 7.1.1 Adverse Events

##### 7.1.1.1 Methodology

AEs will be identified at every contact with a subject throughout the study period beginning with Baseline (Day 1) and after first dose of LAI by direct observation, from assessments of safety parameters, and by asking open-ended, non-leading questions such as “How have you felt since your last visit?” See [Section 8](#) for definitions and a fuller description of the assessment and reporting requirements of AEs.

##### 7.1.1.2 Assessment

All AEs will be recorded on the Adverse Event page of the eCRF. Attempts will be made to determine the start and stop dates of the event, the intensity, causality, treatment, and outcome of

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the event. All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. Any AE that has occurred and resolved before administration of study drug on Day 1 (Baseline) will be documented as an AE for study INS-212.

### 7.1.2 Clinical Laboratory Evaluations

The following clinical chemistry, hematology, and urine parameters comprise the clinical laboratory evaluations:

Clinical Chemistry	Sodium, chloride, potassium, bicarbonate (CO <sub>2</sub> ), magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated >2 ULN), alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate from the Cockcroft-Gault method
Hematology	Hemoglobin, erythrocytes, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets.
Urinalysis	Qualitative analysis of glucose, ketones, nitrites, protein, pH, leukocytes, blood, bilirubin, specific gravity; microscopic examination for cells, casts, and bacteria  Urine pregnancy test for women of child-bearing potential will be performed at the site and results will be entered into the eCRF.
Other Biomarkers	CRP and IL-6

#### 7.1.2.1 Methodology

Blood samples will be drawn with a minimum number of needle insertions to determine clinical chemistry and hematology parameters before administering study drug (if applicable). Details for

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collecting, handling, storing, and transporting blood samples will be provided in the site laboratory manual.

Urine samples will be collected at the same times as blood is drawn.

#### **7.1.2.2 Assessment**

Clinical chemistry and hematology analyses will be performed by a central laboratory; qualitative urinalyses will be performed by a central laboratory, and evaluated microscopically for cells, casts, and bacteria.

#### **7.1.3 Vital Signs**

##### **7.1.3.1 Methodology**

Five-minute sitting blood pressure, pulse rate, body temperature, respiratory rate, and oxygen saturation will be recorded in the eCRF. At visits where study treatment is administered, vital signs will be assessed both pre-dose and post-dose. At visits when the 6MWT is administered, vital signs will be measured before and after subjects walk a prescribed course as far as they can in 6 minutes.

##### **7.1.3.2 Assessment**

Significant findings observed at any time after the first dose of study drug that meet the definition of an AE must be recorded on the Adverse Event page of the eCRF.

Any significant finding that has occurred before administration of the study drug on Day 1 (Baseline) will be documented for study INS-212.

#### **7.1.4 Physical Examination**

##### **7.1.4.1 Methodology**

A physical examination of the head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system, and, as

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appropriate, other body systems will be performed before the administration of study drug. The physical examination will also include weight. All significant findings must be recorded in the eCRF as described below. Any significant finding that has occurred before administration of the study drug on Day 1 (Baseline) will be documented for study INS-212.

#### **7.1.4.2 Assessment**

Significant findings at Baseline (Day 1) and any changes from Baseline (Day 1) prior to first dose at Day 1 must be recorded as part of the INS-212 study. Significant findings made after the Baseline (Day 1) dose of study drug that meets the definition of an AE must be recorded on the Adverse Event page of the eCRF for INS-312.

#### **7.1.5 Concomitant Medications**

The dosage of all concomitant medications should be recorded on the eCRF at every contact with a subject throughout the study period beginning with Baseline (Day 1).

#### **7.1.6 Audiology**

##### **7.1.6.1 Methodology**

Frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz will be evaluated for each ear using air conduction. If audiometry findings are an AE Grade 2 or higher (per the Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0 guideline), an additional audiometric evaluation should be conducted at the next scheduled visit.

##### **7.1.6.2 Assessment**

Significant findings that meet the definition of an AE (including hearing loss of a CTCAE Grade 2 or higher) must be recorded on the AE page of the eCRF. Any significant finding that has occurred before administration of the study drug on Day 1 (Baseline) will be documented for study INS-212.

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## 7.2 SECONDARY ENDPOINT VARIABLES

Please refer to [Section 9.7](#) for more details.

### 7.2.1 Six-minute Walk Test

#### 7.2.1.1 Methodology

A 6MWT of exertional capability will be performed per ATS guidelines (<http://ajrccm.atsjournals.org/cgi/content/full/166/1/111>). Overall fatigue and dyspnea (Borg scale) will be measured before and after subjects walk a prescribed course as far as they can in 6 minutes.

#### 7.2.1.2 Assessment

The distance achieved will be recorded in the eCRF.

### 7.2.2 Sputum Collection, Transport, and Assessment

Pre-dose expectorated or induced sputum specimens (approximately 3 mL) are required at every scheduled visit during the treatment phase. To improve the probability of obtaining a good sputum specimen, it is recommended that at least 2 sputum samples will be obtained from each subject for each study visit at which sputum is collected. One sputum sample will be collected on one of the 2 days prior to a scheduled visit. Subjects will refrain from administering LAI on the days' sputum is obtained, starting 2 days prior to the scheduled visit, even if a spontaneous sputum cannot be obtained by the subject at home. If a subject is unable to produce sputum spontaneously, one induced sputum specimen at the site will be acceptable. At the scheduled visit, once sputum is collected (spontaneously or by induction), the administration of LAI can recommence. Sites are encouraged to notify subjects by telephone of this procedure 3 days prior to their scheduled visit. If a subject is unable to produce sputum independently, sputum may be induced as described in [APPENDIX 1](#) at the clinical site only, if these suggestions are safe for the subject. If a subject is still unable to produce sputum despite reasonable efforts, this will be recorded as a negative culture result at that time point.

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Sterile, leak proof, non-wax, disposable plastic containers labeled with 2 subject identifiers will be used to collect specimens aseptically to avoid contamination. Sputum samples should be refrigerated, not frozen, until shipped to the central microbiology lab within 2 days of collection to avoid overgrowth by contaminating normal flora. No fixative or preservatives are to be used with sputum samples. Detailed instructions for collecting, processing, and shipping sputum specimens will be provided in the site laboratory manual.

### 7.2.3 Microbiological Assessment

Sputum specimens will be cultured in liquid media in addition to solid media (agar). If results are negative on agar, the liquid media will be held for 6 weeks before reporting as culture negative.

Standard antibiotic sensitivity testing using minimum inhibitory concentrations will be routinely performed on bacterial isolates (Clinical and Laboratory Standards Institute [CLSI] M48-A and NCCLS M24-A) (Forbes, 2008). All mycobacterial isolates will be banked for subsequent determination of amikacin susceptibility and selective molecular typing (Prammananan, 1998). The sputum culture reports will be provided to the Investigators as they become available.

Only MAC isolates from sputum cultures will be analyzed. Isolates of MAC will be identified to complex, using a commercial RNA probe (Gen-Probe/Hain CM Line Probe) and subsequently identified to sub-species (*M. avium*, *M. intracellulare*, MAC “X” group) using molecular methodology (Cousins, 1996).

New potential respiratory pathogens that may emerge during the treatment period will not be reported in the culture report. These separate pathogens will be managed by the individual Investigator.

A converter is defined as a subject who has 3 consecutive monthly MAC-negative sputum cultures at any time during the study.

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) after achieving culture conversion. For subjects who convert and subsequently have a positive MAC sputum culture, analyses will be conducted to confirm

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whether the positive MAC culture is due to a different MAC species or strain acquired by the subject, or due to a relapse of the same MAC species or strain as observed at Baseline (Day 1). The MAC species will be identified by sequencing the gene for the 16S rRNA subunit. If the MAC isolates identified after conversion are a different species, it will be determined that the subject acquired a different MAC species, rather than had a relapse. If the same species as seen at Baseline (Day 1) is observed, then DNA fingerprinting (based on a variable number of tandem repeat [VNTR]) will be conducted to identify the strain to determine whether the subject has acquired a different MAC strain. For subjects who had a negative sputum culture at Baseline (Day 1) and did not achieve culture conversion, the MAC species will be compared to the Baseline (Day 1) species determined in INS-212.

### 7.3 EXPLORATORY ENDPOINT VARIABLES

Please refer to [Section 9.7](#) for more details.

#### 7.3.1 St. George's Respiratory Questionnaire

##### 7.3.1.1 Methodology

The SGRQ is a self-administered questionnaire that has been validated in subjects with airways disease, specifically in subjects with BR ([Jones, 1991](#); [Jones, 1991](#); [Wilson, 1997](#)). The SGRQ assesses health-related quality of life in subjects with chronic pulmonary disease by evaluating 3 health domains: symptoms (distress caused by respiratory symptoms); activity (effects of disturbances to mobility and physical activity); and impacts (the effect of disease on factors such as employment, personal control of one's health, and need for medication).

##### 7.3.1.2 Assessment

A composite total score is derived as the sum of domain scores for symptoms, activity, and impact, with 0 the best possible score and 100 the worst possible score. A reduction in score of 4 units is generally recognized as a clinically meaningful improvement in quality of life.

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### 7.3.2 EQ-5D-3L

#### 7.3.2.1 Methodology

The EQ-5D-3L, is a preference-based, (multi-attribute) generic health-status classification instrument that generates a composite score reflecting the preference value associated with a given health state. The system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no health problems, moderate health problems, and extreme health problems. Current general health is also scored using a visual analog scale.

#### 7.3.2.2 Assessment

The health state is reported with a 5-digit descriptor ranging from 11111, representing the best case, to 33333, representing the worst case. The score for each domain of the EQ-5D-3L will be reported in the eCRF.

### 7.3.3 Healthcare Resource Utilization

The changes to normal daily activities (i.e. number of days missed from work, on disability, amount of sleep, etc.), NTM related and non-NTM related visits to healthcare providers, Emergency Room (ER) visits, and hospitalizations including days in the hospital, and days in Intensive Care Units (ICU) will be captured.

### 7.3.4 Computed Tomography Scan of Chest

Chest CT scans will be evaluated as part of the chest CT Scan Sub-Study at sites that are willing and have been approved for the sub-study. The objective of the CT Scan Sub-Study will be to compare assessments of the chest CT scans, read by a trained medical professional, from Baseline (Day 1) to the EOT visit provided a chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available. Details regarding the chest CT Scan Sub-Study are described in [APPENDIX 3](#). All Japanese subjects in Japan will participate in the Japan specific CT scan sub-study, which also has a safety objective and a Month 6 CT scan. Details of the Japan specific CT Scan Sub-Study are described in [APPENDIX 4](#).

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#### 7.4 APPROPRIATENESS OF MEASUREMENTS

Data will be collected using standard methods, widely used and generally regarded as reliable accurate, and relevant.

### 8 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

#### 8.1 DEFINITION OF AN 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.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Examples of AEs include one of the following or a combination of 2 or more of these factors:

- A new sign, symptom, illness, or syndrome
- Worsening of a concomitant illness
- An effect of investigational product, including comparator or concomitant medication
- An effect of an invasive procedure required by the protocol
- An accident or injury
- Laboratory abnormality that the Investigator considers clinically relevant

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Surgical measures planned prior to study enrollment are permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

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## 8.2 DEFINITION OF A SERIOUS ADVERSE EVENT

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
  - NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. The IB serves as the Reference Safety Information for the determination of expectedness of AEs. The Sponsor will reference the current IB when assessing the expectedness of adverse events for reporting to Health Authorities/IRB/EC/Investigators.

### 8.2.1 Assessment of Intensity

Each AE will be graded per CTCAE v4.0, as applicable. All other laboratory and clinical AEs that occur in a subject will be assessed for severity and classified using the categories below.

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- **Grade 1 (Mild):** Event requires minimal or no treatment and does not interfere with the subject's daily activities.
- **Grade 2 (Moderate):** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe):** Event interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Life threatening):** Any adverse drug experience that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death).
- **Grade 5 (Death)**

### 8.2.2 Assessment of Causality

The Investigator who identifies an AE will determine the causality of each based on the temporal relationship to administration of study drug and clinical judgment. The degree of certainty about causality will be graded using the categories below.

**Definitely Related:** A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

**Probably Related:** A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

**Possibly Related:** A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could

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reasonably have been produced by several other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

**Not Related:** A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

### 8.2.3 Assessment of Outcome

The Investigator will record the outcome of the AE as either resolved or ongoing on the AE page of the eCRF. AEs of unknown outcome will be considered as ongoing for purposes of AE reporting.

## 8.3 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are those known to be attributed to parenteral amikacin:

- nephrotoxicity, including elevation of serum creatinine, albuminuria, presence of red and white cells, casts, azotemia, and oliguria
- ototoxicity affecting the eighth cranial nerve resulting in hearing loss, loss of balance, or both.
- neuromuscular disorders
- allergic alveolitis
- bronchospasm
- hemoptysis

Cough is often associated with drug products that are nebulized. To properly characterize AEs of cough, specific details regarding AEs of cough will be reported in the AE eCRF pages.

It is expected that subjects in this study will experience a large number of pulmonary exacerbation events due to their underlying lung condition(s). Pulmonary exacerbation will be defined based on the Investigators best clinical judgment. Details of the type of exacerbation should be provided on the AE eCRF.

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## 8.4 REPORTING REQUIREMENTS

### 8.4.1 Adverse Events

All AEs will be reported on the Adverse Events page of the eCRF. All ongoing AEs from the INS-212 study will be documented as medical history for INS-312. Any AE that has occurred and resolved before administration of the study drug on Day 1 (Baseline) will be documented as an AE for study INS-212.

### 8.4.2 Serious Adverse Events

All SAEs, regardless of causality, must be reported to an organization delegated by the Sponsor (PrimeVigilance will be responsible for SAE reporting for INS-312) on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours. Study-specific email, phone, and fax number for SAE reporting are presented in the Study Reference Manual.

Unexpected drug-related SAEs, as assessed by Sponsor or authorized person qualify for expedited reporting, will be reported to the IRB/EC, regulatory authorities, participating Investigators. Suspected unexpected serious adverse reactions (SUSARs), in accordance with all applicable global laws and regulations, will be cross reported as required. A SUSAR is a Serious Adverse Reaction (SAR), which is suspected to be caused by the investigational medicinal product and which is unexpected i.e. its nature or severity is not consistent with the information in the relevant source documents. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (i.e. for the FDA these are reported in the Investigational New Drug [IND] annual report and for EMA these are reported in the Development Safety Update Report [DSUR]).

#### 8.4.2.1 Pregnancy

Any pregnancy that occurs during any phase of the study must be reported to PrimeVigilance within 24 hours of learning of the pregnancy using a Clinical Study Pregnancy Form.

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The study treatment should be discontinued and the pregnancy should be followed to term. The details of pregnancy outcome must also be reported, including details of birth, the presence or absence of birth defects, congenital abnormalities or maternal and newborn complications, or whether termination was spontaneous or voluntary.

#### 8.4.2.2 Overdose

An overdose is defined as a dose greater than the dose level evaluated in this study as described in [Section 5.4](#) that results in clinical signs and symptoms. In the case of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug used in the study. Such document(s) may include, but not limited to, the IB ([LAI IB, 2016](#)) and approved product labeling for Amikacin.

### 8.5 FOLLOW-UP OF ADVERSE AND SERIOUS ADVERSE EVENTS

All SAEs, including those ongoing at EOS, must be followed until resolution or stabilization or until otherwise explained.

### 8.6 REGULATORY ASPECTS

The Sponsor has a legal responsibility to notify the FDA, National Competent Authorities and Central Ethics Committees of the European Union, and all other foreign regulatory agencies, as well as all sites, about the safety of the drug. As applicable, the Investigator must comply with local requirements for reporting to Institutional Review Board/Independent Ethics Committee (IRB/EC).

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/EC review and regulatory inspection(s), providing direct access to source data/documents. Copies of the notification to the ethics committee must be sent to the Sponsor.

The Investigator will provide a properly completed and signed Form FDA-1572 (Statement of Investigator) to Insmmed prior to the conduct of the study.

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## 9 STATISTICS

### 9.1 SAMPLE SIZE

There is no sample size determination as this study follows the INS-212 study; eligible subjects who consent after Month 6 and complete the EOT visit of the INS-212 study will determine the sample size of this study.

### 9.2 STRATIFICATION

Not applicable.

### 9.3 RANDOMIZATION AND BLINDING

Not applicable.

### 9.4 STATISTICAL METHODOLOGY

A statistical analysis plan (SAP) will be developed describing details regarding all analyses, tables, figures, and data listings. All analyses will be performed using SAS®.

#### **First and Latter Analyses**

The INS-312 study will comprise of two analyses. The first analyses will assess the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6; the time to culture conversion (defined by the date of the first of at least 3 consecutive monthly culture specimens that are MAC negative); and the mean change from Baseline in the 6MWT distance by Month 6 of the study, as well as the safety and tolerability of LAI. The latter analyses will be the final analyses at the completion of the study and will include all other endpoints.

### 9.5 ANALYSIS POPULATIONS

The safety population is the set of all enrolled subjects who received at least 1 dose of LAI.

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## 9.6 SAFETY ANALYSIS

The safety endpoints are the frequency of TEAEs, TEAEs leading to withdrawal from study, treatment-emergent SAEs, AEs of special interest, clinically significant abnormal laboratory test results, and vital signs measurements. The safety analysis will be performed for the safety population.

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). AEs starting between first study drug administration and 1 month after last study drug administration will be regarded as treatment emergent (TEAE).

The number and percentage of subjects with TEAEs, TEAEs leading to withdrawal from study, and treatment-emergent SAEs will be tabulated by System Organ Class and Preferred Term overall and by the assigned treatment arm in INS-212. Furthermore, the incidence of TEAEs by worst grade of severity will also be tabulated by System Organ Class and Preferred Term overall and by assigned the treatment arm in INS-212.

AEs that are not treatment-emergent will be listed.

For all other safety data (vital sign measurements, clinical laboratory values, and physical examination findings) 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 assigned treatment arm in INS-212 using descriptive statistics.

## 9.7 SECONDARY AND EXPLORATORY EFFICACY ANALYSIS

Proportion of subjects achieving negative sputum culture conversion by Month 12/EOT and Month 6 will be summarized overall and by previous treatment arm in INS-212. Kaplan Meier estimates for the distribution of time to culture conversion will be constructed for the treatment arms in INS-212. The changes in 6MWT distance, SGRQ, SGRQ-Part II, EQ-5D-3L, and subject-reported symptoms of NTM will be summarized across all the study visits overall and by the previous treatment arm in INS-212 for the safety population. The efficacy analysis will be performed for the safety population.

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CT scan data will be summarized overall by previous treatment arm in INS-212 for both subjects in the CT scan sub-study and subjects in the Japan specific CT scan sub-study.

## 10 DATA MANAGEMENT

### 10.1 SOURCE DOCUMENTS

Study data will be collected on source documents. The Principal Investigator (PI) is responsible for assuring that collected data are complete and accurate. Source documentation (the point of initial recording of a piece of data) should support data collected on the eCRF. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study.

### 10.2 DATA COLLECTION AND CASE REPORT FORM MONITORING

All data obtained for this study will be entered into a local regulation (i.e. 21 CFR Part 11 in the USA) compliant Data Management System provided by Insmmed or its designee. These data will be recorded with an Electronic Data Capture (EDC) system using eCRFs. The Investigator will ensure the accuracy and completeness of the data reported to the Sponsor. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. Data reported in the eCRFs should be consistent with and substantiated by the subject's medical record and original source documents. The eCRF data will be monitored by the Sponsor or designee. The final, completed eCRF Casebook for each subject must be electronically signed and dated by the Principal Investigator (PI) within the EDC system to signify that the Investigator has reviewed the eCRF and certifies it to be complete and accurate.

The Sponsor will retain the final eCRF data and audit trail. A copy of all completed eCRFs will be provided to the Investigator.

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### 10.3 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Insmmed. It is the responsibility of Insmmed to inform the Investigator when these documents no longer need to be retained.

## 11 ETHICAL CONSIDERATIONS

A copy of the protocol, informed consent forms, other information to be completed by subjects, such as questionnaires and any proposed advertising or recruitment materials, will be submitted to the regulatory authority(ies) and IRBs/ECs in accordance with country-specific requirements.

All subsequent amendments to the protocol, informed consent documents, and other study documentation referenced above must be submitted and approved in accordance with country-specific requirements.

Periodic study status reports will be submitted to the IRBs/ECs in accordance with country-specific regulations. Where applicable, the Investigator will be responsible for obtaining IRB/EC approval of the annual continuing review throughout the duration of the study.

The PIs will notify the local IRBs/ECs of violations from the protocol and SAEs.

Subjects will be informed that medical care will not be affected by their agreement or refusal to participate in this study, and that they are free to withdraw from the study at any time without prejudice to the clinician patient relationship.

The study will be conducted per the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), and the ICH E6 Guideline for Good Clinical Practice (GCP). The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements as

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applicable. Throughout the study, the Sponsor and its designee will work with the Investigator(s) to ensure proper study protocol implementation and adherence to regulatory requirements as listed in the study protocol.

### **11.1 GOOD CLINICAL PRACTICE**

This study is to be conducted per globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice), in agreement with the Declaration of Helsinki and in keeping with local regulations.

### **11.2 DELEGATION OF INVESTIGATOR DUTIES**

The Investigator must ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator must maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

### **11.3 PATIENT INFORMATION AND INFORMED CONSENT**

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

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## 12 ADMINISTRATIVE PROCEDURES

### 12.1 FINANCIAL DISCLOSURE BY INVESTIGATOR

The disclosed financial interest of the Investigator must be collected before screening of the first subject and updated if applicable, at study completion and 1 year following overall study completion. The Investigator should promptly update this information if any relevant changes occur during this period.

### 12.2 STUDY REGISTRATION AND RESULTS DISCLOSURE

The Sponsor may provide study information for inclusion in national registries per local regulatory requirements.

Results of this study will be disclosed per the relevant national regulatory requirements.

### 12.3 STUDY FILES AND MATERIALS

Before the start of any study related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by the Sponsor (or delegate) and the Investigator. An Investigator Study File prepared by the Sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigators at each site will be included in the Investigator Study File. The respective files will be kept and updated by the Sponsor (or delegate) and the Investigator, as applicable.

Study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the Sponsor's study monitor (or delegate) to determine that required documentation is present and correct.

The study may be audited by qualified delegates from the Sponsor or a competent regulatory authority ([Section 12.11](#)).

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#### 12.4 USE OF STORED SAMPLES AND DATA

Serum samples from the IL-6 analysis will be stored at the aforementioned laboratory for a period of up to 2 years after the completion (termination) of the study, or longer if required by the institution participating in the study, to see whether there may be indicators associated with NTM lung infections and for other exploratory analyses for an NTM lung infection (no genetic testing or analysis will be performed on blood samples collected). Mycobacterial isolates will be stored for a period of up to 2 years after the completion (termination) of the study, or longer if required by the institution participating in the study and will be used for future selective susceptibility testing for correlation with microbiologic and clinical response and for molecular typing of serial isolates to identify multiple strains within individuals that might influence treatment outcome. Stored samples will be labeled with study and subject information and kept in a locked room with limited access. Electronic data will be kept in password-protected computers at the laboratory and then transferred to the Sponsor or Clinical Research Organization (CRO), as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Sponsor and IRB/EC approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol.

Any loss or unanticipated destruction of samples (e.g., freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to the Sponsor and the IRB/EC.

At any time, subjects may inform the Investigator that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed and report the disposition of samples to the requesting subjects and the IRB/EC.

#### 12.5 Disposition of Stored Samples and Data

Access to stored samples will be limited by using a locked room. All samples stored will be labeled with the subject's study identification information. Data will be kept in password-protected computers at the laboratory and then transferred to the vendor for data

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analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, other Investigators may wish to study these samples and/or data. In that case, IRB/EC approval and Sponsor approval must be obtained before any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior Sponsor and IRB/EC approval.

Additionally, subjects may decide at any point not to have their samples stored for a period of up to 2 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the subject and to the IRB/EC. This decision will not affect the subject's participation in this protocol.

## **12.6 Initiation of Study**

Before the start of the study at each study site, the Sponsor's study monitor (or delegate) will visit the study site to ensure adequacy of the facilities and to discuss responsibilities regarding study protocol adherence with the Investigator and other personnel involved in the study.

The Investigator may not enroll any subject into the study before the Sponsor has received written approval or a favorable opinion from the EC or IRB for conducting the study and a formal meeting has been conducted by the Sponsor's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the eCRF.

## **12.7 Subject Reimbursement, Liability, and Insurance**

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise because of this study being conducted are governed by the applicable legal requirement(s).

The Sponsor will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

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If required by local law, subjects taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

### 12.8 Subject Identification and Confidentiality

Subject names will not be supplied to the Sponsor. A subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor. All records will be kept confidential to the extent provided by federal, state, and local laws. The subjects will be informed that representatives of the Sponsor, IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

### 12.9 Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol, eCRF, IB, and any study-related materials with the Investigators and their staff. During the study, the study Sponsor monitor or its designee will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for per specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center. The study Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed per the study-specific monitoring plan.

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### 12.10 Study Plan Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor, before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies), central ECs, and local IRBs/ECs. Copies of the applicable written approvals must be given to the site monitor or their designee.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the study Sponsor or its agent should be notified and the applicable regulatory authority(ies)/central ECs/local IRBs/ECs should be informed within 10 working days. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/central EC/local IRB/EC approval, but the regulatory authority(ies)/central ECs/local IRBs/ECs must be kept informed of such administrative changes in accordance with country-specific requirements.

### 12.11 Audits and Inspections

Domestic and foreign regulatory authorities, the IRB/EC, and an auditor authorized by the Sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection if subject names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform the study Sponsor, immediately that this request has been made.

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### 12.12 Use of Data and Publications

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of the study Sponsor. Authorship will be determined by mutual agreement. For multi-center studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by the study Sponsor and statisticians, and not by the Investigators themselves. Investigators participating in multi-center studies agree not to present data gathered from a single center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and study Sponsor.

The study Sponsor must receive copies of any intended communication at least 60 days in advance of submission for publication. The study Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Sponsor may request additional time to obtain appropriate intellectual property protection. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as the study Sponsor personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a clinical study report.

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## 14 APPENDICES

### APPENDIX 1 SPUTUM INDUCTION SUGGESTIONS

#### **Introduction**

Collection of good sputum samples is critical to the success of this study. Sputum samples will be collected at the clinical site and by the subject at home. To facilitate obtaining good sputum samples during the study visits at the clinic, sputum induction will only be performed at the clinical study site if the subject is unable to expectorate approximately 3.0 mL of sputum.

#### **Purpose**

The purpose of this appendix is to provide suggestions to the clinical sites for obtaining a sputum sample by induction if the subject is unable to expectorate a sputum sample on their own or after chest percussion.

#### **Suggested Equipment**

- Standard handheld nebulizer used in the clinic or the subject can be asked to bring the nebulizer they use at home for pulmonary hygiene
  - The nebulizer should be thoroughly disinfected to ensure no cross-contamination
  - **DO NOT** use the subject's PARI eFlow® nebulizer for sputum induction
- Sputum specimen containers with label – sputum collection tube provided by central laboratory
- Sodium chloride solution (Saline)
- Standard clinic supplies (e.g., disinfectant/germicidal/alcohol wipes, tissues, paper towels, etc)

#### **Procedure**

##### *General Instructions:*

- At the clinic, sputum induction should occur before administration of study drug.

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- Sputum induction should occur in a private, contained room. Specific processes in place at the clinic to prevent contamination and ensure sterilization before and after sputum induction should be followed.
- Clinic personnel should wear gloves and a mask during the entire procedure.
- Only one subject should be induced at a time.
- All collection containers should have a sputum collection label clearly completed with subject identifiers, visit name, date and time.
- The subject should have been instructed to not eat at least within 1 hour of sputum induction procedures.
- Explain to the subject that the purpose of this procedure is to help him/her cough up a sputum sample and that the success of the procedure is dependent on the subject's active participation.

#### *Inhalation and Collection Procedures:*

- The induction procedure should start by utilizing lower concentrations of saline (e.g., 3%) based on the Investigator's preference.
- Approximately 3-6 mL of the selected saline should be placed in the nebulizer.
- The subject should be sitting up or in a semi-fowler position.
- The subject may wear a nose clip during the nebulization.
- The subject should breathe slowly and deeply through the nebulizer mouthpiece inhaling the salt water mist. Remind the subject to not breathe quickly but to have slow, deep breaths pausing at peak inspiration to allow deposition of particles.
- The nebulization time is 10 minutes.
- At the end of this time, the subject should take a few deep breaths, swallow the extra saliva in his/her mouth and try to cough up a sputum sample.
- The subject should be encouraged to cough forcefully using the deep coughing method and/or "huffing" cough method.
- All sputum should be deposited in the container. The specimen container should not be opened until the specimen is ready to be deposited. The container should be closed immediately after depositing the sample.
- The sputum sample should be approximately 3 mL - slightly below the bottom line (5 mL) on the collection container.

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- If a sufficient sputum sample is not collected and the subject appears to be tolerating the induction procedure well, the subject can complete another 10-minute nebulization period.
  - If a second 10-minute nebulization period is required, the recommendation is to increase the sodium chloride concentration (i.e., if 3% was used first then 7% should be used for the subsequent nebulization; if 7% was used first then 10% should be used for the subsequent nebulization).
  - Closely monitor the subject for tolerability issues or side effects.
  - No more than two 10-minute nebulization periods should be completed.
- The sputum sample should be refrigerated until it is sent to the microbiology laboratory.

### Side Effects

- The subject may experience side effects from the sputum induction procedure. The most common side effects include:
  - coughing
  - wheezing
  - lightheadedness
  - shortness of breath
  - sore throat
  - nausea
  - headache
  - chest tightness
- Other possible side effects include hyperventilation or bronchospasm. For bronchospasm, ensure subject receives the necessary medical management.

### Miscellaneous

- If the subject needs to expectorate during nebulization, turn off the nebulizer and allow the subject to cough up sputum into the container. If a sufficient specimen is not collected, the subject should then resume the nebulization to complete the 10-minute nebulization duration.
- The subject should be encouraged to blow his/her nose as often as needed during the induction procedure to help prevent nasal secretions from becoming mixed with sputum specimen.

Protocol Amendment 3.1: 25 May 2017

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## APPENDIX 2      CONTENT OF STUDY DRUG LABEL

**Table 14-1      Content of Study Drug Label**

Number	Label requirements	Specific Label information
1	Pharmaceutical dosage form, route of administration, and in the case of open-label study, the name/identifier and strength/potency	590 mg Liposomal Amikacin (aminoglycoside) nebulizer suspension for inhalation using PARI eFlow® nebulizer
2	Quantity of the dosage unit	590 mg
3	Protocol number	INS-312
4	Subject Identifier	Subject specific
5	Human subject number	Subject specific
6	Lot number	Subject specific
7	Re-assay/expiration date	Subject specific
8	Caution statement	For clinical trial use only.
9	Storage conditions	Store between 2-8 °C. Do not freeze. Protect from heat.
10	Sponsor identification, name, address	GLOBAL CLINICAL AND REGULATORY AFFAIRS Insmmed Incorporated 10 Finderne Avenue, Building 10 Bridgewater, NJ 08807
11	Direction for use	This product should only be used after appropriate training. Shake well.
12	Statement: <i>"Keep out of sight and reach of children"</i>	Keep out of sight and reach of children.

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**APPENDIX 3 CT SCAN SUB-STUDY**

**Sub-study of INS-312:**  
***CT Scan Sub-Study***

**CT Scan Sub-Study Protocol**

**Version Date: 11 March 2016**

**Name of Approver**

[REDACTED]

**Title of Approver**

[REDACTED]

**Signature of Approver**

[REDACTED]

**Date:** 25 May 2017

Insmed Incorporated  
10 FINDERNE AVENUE, BUILDING 10  
BRIDGEWATER, NJ 08807-3365

Protocol Amendment 3.1: 25 May 2017

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**SIGNATURE PAGE FOR THE INVESTIGATOR**

**Protocol Number**

**INS-312**

I have read the INS-312 CT Scan Sub-Study protocol and agree that it contains all necessary details for carrying out this sub-study. I will conduct the sub-study as outlined herein and will complete the sub-study within the time designated, in accordance with all stipulations of the sub-study protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the INS-312 CT Scan Sub-Study protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this sub-study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the sub-study.

I will use only the informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/EC responsible for this sub-study.

I agree that the Sponsor, Insmmed Incorporated, or its representatives shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name of Insmmed Incorporated, or study drug code in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this sub-study protocol, to any amendment to the sub-study protocol, or to the performance of this sub-study, without the prior written consent of Insmmed Incorporated.

**Name of Approver**

Type or print name of signer.

[Redacted Name]  
[Redacted Signature]  
06/15/2017

Signature of Approver \_\_\_\_\_

Date: mm/dd/yyyy

Protocol Amendment 3.1: 25 May 2017

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**Confidential**

### **Introduction**

LAI is a novel formulation of amikacin that is encapsulated in liposomes comprised of DPPC and cholesterol (naturally occurring lipids in the lung) to allow for effective delivery in the lung, leading to high concentrations of the drug at the target sites of infection, with low systemic levels. In clinical study TR02-112 LAI in addition to standard background therapy was statistically superior at the end of the double-blind period (Day 84) for achieving a negative sputum culture compared to those who received placebo in addition to standard background therapy.

Study INS-312 CT-scan sub-study will evaluate whether there are any radiographical changes that occur in subjects who have failed to achieve culture conversion in INS-212 and started or continued on treatment with LAI in INS-312.

### **Sub-Study Objective**

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

### **Sub-Study Design**

Eligible subjects must be enrolled into the INS-312 study. At Baseline (Day 1), any subject who has signed the informed consent for this chest CT Scan Sub-Study will participate; there is no maximum number of subjects that can participate. At the latest, the informed consent and the subject's Baseline chest CT scan must be collected no later than 2 weeks after the subject's first dose of LAI in the INS-312 study. A prior chest CT scan may be used as a subject's Baseline measurement if this CT scan was obtained at the EOT visit in INS-212, or within 6 months from the subjects Baseline (Day 1) study visit. All subjects in this chest CT Scan Sub-Study will have their follow-up chest CT scan on 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.

### **Sub-Study Endpoint**

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## 1. Radiological changes in CT scan at EOT, within a sub-set of subjects

### **Sub-Study Population**

Only sites that have agreed to and can perform the chest CT scans will participate in this sub-study once they have IRB/EC approval for the main INS-312 and for this chest CT Sub-Study. Subjects must provide written informed consent for both the main INS-312 study and for this sub-study.

### **Sub-Study Procedures**

On Day 1 (+14 days) subjects will be asked to provide informed consent for this sub-study. Once the informed consent has been signed the subject should have a chest CT scan performed at Baseline (Day 1) (the CT scan performed at the EOT visit in INS-212 or a prior CT scan that was obtained within 6 months prior to signing the informed consent may be used for Baseline). A second chest CT scan will have performed at the EOT visit, if more than 6 months have elapsed since their last CT scan; this includes any subject that prematurely discontinues the study. High resolution CT scan is preferred, if available.

All chest CT scans will be read locally and a description of findings for each scan will be entered into the eCRF page. An overall assessment of improved, worsening, or no change from previous scan will be reported for all scans after the subject's Baseline scan. All chest CT scans must be made available to the Sponsor to be stored as study source documentation.

Protocol Amendment 3.1: 25 May 2017

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**Table 14-2 Schedule of Events for INS-312 CT Scan Sub-Study**

<b>INS-312 CT Scan Sub-Study</b>		
	<b>Baseline</b>	<b>EOT</b>
	<b>(V1)</b>	<b>(V13)</b>
<b>Visit Window</b>	<b>(-6 months to +14 Days)</b>	<b>(±14 days)</b>
<b>Informed Consent<sup>a</sup></b>	<b>X</b>	<b>-</b>
<b>CT Scan of Chest<sup>b</sup></b>	<b>X</b>	<b>X</b>

<sup>a</sup> This may be a separate informed consent from the INS-312 main study.

<sup>b</sup> Subjects will have a chest CT scan at Baseline (Day 1), unless one was already obtained at the INS-212 EOT Visit, or a prior CT scan was obtained within the prior 6 months. 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.

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APPENDIX 4 JAPAN SPECIFIC CT SCAN SUB-STUDY

## Sub-study of INS-312:

### *Japan Specific CT Scan Sub-Study*

CT Scan Sub-Study Protocol

Version Date: 11 March 2016

Name of Approver

[REDACTED]

Title of Approver

[REDACTED]

Signature of Approver

[REDACTED]

Date: 25 May 2017

Insmed Incorporated  
10 FINDERNE AVENUE, BUILDING 10  
BRIDGEWATER, NJ 08807-3365

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**SIGNATURE PAGE FOR THE INVESTIGATOR****Protocol Number**

INS-312

I have read the INS-312 Japan Specific CT Scan Sub-Study protocol and agree that it contains all necessary details for carrying out this sub-study. I will conduct the sub-study as outlined herein and will complete the sub-study within the time designated, in accordance with all stipulations of the sub-study protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the INS-312 Japan Specific CT Scan Sub-Study protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this sub-study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the sub-study.

I will use only the informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/EC) and will fulfill all responsibilities for submitting pertinent information to the IRB/EC responsible for this sub-study.

I agree that the Sponsor, Insmmed Incorporated, or its representatives shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name of Insmmed Incorporated, or study drug code in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this sub-study protocol, to any amendment to the sub-study protocol, or to the performance of this sub-study, without the prior written consent of Insmmed Incorporated.

**Name of Approver**

Type or print name of signer.

Signature of Approver \_\_\_\_\_

Date: mm/dd/yyyy

Protocol Amendment 3.1: 25 May 2017

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## **Introduction**

LAI is a novel formulation of amikacin that is encapsulated in liposomes comprised of DPPC and cholesterol (naturally occurring lipids in the lung) to allow for effective delivery in the lung, leading to high concentrations of the drug at the target sites of infection, with low systemic levels. In clinical study TR02-112 LAI in addition to standard background therapy was statistically superior at the end of the double-blind period (Day 84) for achieving a negative sputum culture compared to those who received placebo in addition to standard background therapy.

Study INS-312 Japan specific CT-scan sub-study will evaluate whether there are any radiographical changes that occur in Japanese subjects who have failed to achieve culture conversion in INS-212 and started or continued treatment with LAI in INS-312.

## **Sub-Study Objectives**

1. To compare assessments of radiographs, read by a trained medical professional, from Baseline (Day 1) in CT scans at EOT in Japanese subjects from sites in Japan
2. To assess the safety of LAI by CT scans (at 6 month intervals) in subjects from sites in Japan

## **Sub-Study Design**

Eligible subjects must be enrolled into the INS-312 study. The informed consent for this Japan specific CT Scan Sub-Study is included in the informed consent for the main study. All Japanese subjects in Japan will participate in this sub-study. There is no maximum number of subjects that can participate. At the latest, the subject's Baseline chest CT scan must be collected no later than 2 weeks after the subject's first dose of LAI in the INS-312 study. A prior chest CT scan may be used as a subject's Baseline measurement if this CT scan was obtained at the Month 6 visit in INS-212, or within 6 months from the subject's Baseline (Day 1) study visit. Subjects will also have CT scans at Month 6 and at the EOT visits, provided the last CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available.

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**Sub-Study Endpoint**

1. Radiological changes in CT scan at EOT
2. Six-month interval safety assessment for subjects enrolled at sites in Japan

**Sub-Study Population**

All Japanese subjects at all study sites in Japan will participate in this sub-study once they have IRB/EC approval. The informed consent for this Japan specific CT Scan Sub-Study is included in the informed consent for the main study. There are no separate inclusion or exclusion criteria for this sub-study.

**Sub-Study Procedures**

The first chest CT scan should be performed at Day 1 or up to 14 days after the first dose of LAI (the CT scan performed at the Month 6 visit in INS-212 or a prior CT scan that was obtained within 6 months prior to Day 1 may be used for Baseline). Additional CT scans will be obtained at the Month 6 and EOT visits, provided the last CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available.

All chest CT scans will be read locally and a description of findings for each scan will be entered into the eCRF page. An overall assessment of improved, worsening, or no change from previous scan will be reported for all scans after the subject's Baseline scan. All chest CT scans must be made available to the Sponsor to be stored as study source documentation.

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**Table 14-3 Schedule of Events for INS-312 Japan Specific CT Scan Sub-Study**

<b>INS-312 Japan Specific CT Scan Sub-Study</b>			
	<b>Baseline (Day 1)</b>	<b>Month 6</b>	<b>EOT</b>
	<b>(V1)</b>	<b>(V7)</b>	<b>(V13)</b>
<b>Visit Window</b>	<b>(-6 months to +14 Days)</b>	<b>(±3 days)</b>	<b>(±14 days)</b>
<b>Informed Consent<sup>a</sup></b>	X	-	-
<b>CT Scan of Chest<sup>b</sup></b>	X	X	X

<sup>a</sup> In Japan, all subjects will participate in the CT scan sub-study. Informed consent for this sub-study is included in the informed consent of INS-312 main study.

<sup>b</sup> A prior chest CT scan may be used as a subject's Baseline (Day 1) measurement if this CT scan was performed at the Month 6 visit in INS-312 or obtained within 6 months from the subject's Baseline (Day 1) visit. Subjects will have their follow-up chest CT scan at the Month 6 and EOT visits, provided the last chest CT scan was not obtained within the prior 6 months. High resolution CT scan is preferred, if available.

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