Official Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis – The Willow Study

NCT Number: NCT03218917

Document Dates: SAP Version 1.0: 10-January-2020

Statistical Analysis Plan

Document Type:	Template	Document ID:	03.007A.03
Issue Date:	02 MAY 2016	Effective Date:	30 MAY 2016

Sponsor Name:	**Insmed Incorporated**
Protocol Number and Title:	**INS1007-201 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis - The Willow Study**
Original Protocol:	**21 June 2017**
Protocol Amendment numbers and dates	**Amendment 1.0, 24 August 2017** **Amendment 2.0, 12 March 2018** **Amendment 3.0, 27 April 2018** **Amendment 4.0, 24 September 2018**
Syneos Health Project Code:	**1009113**
Author(s):	[redacted]
SAP Version:	Version 1.0
SAP Version Date:	09-January-2020

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
0.1	13-Oct-2017	[redacted]	Initial Release Version based on protocol amendment 1.0
0.2	29-Jan-2018		Changes made based on sponsor's comments
0.3	16-May-2018		Incorporated changes from protocol amendment 2.0 and changes made based on sponsor's comments
0.4	27-Jun-2018		Incorporated changes from protocol amendment 3.0 and changes made based on sponsor's comments
0.5	02-Nov-2018		Incorporated changes from protocol amendment 4.0 and changes made based on sponsor's comments
0.6	30-Nov-2018		Added analyses for 3 exploratory endpoints in section 8.4. Removed the exploratory endpoint #14 (related to biomarkers) from section 4.3. Added Appendix B to clarify the calculation of Bronchiectasis Severity Index. Changes made based on sponsor's comments
0.7	20-Dec-2018		Added 2 more sensitivity analyses for the primary endpoint in section 8.2.2. Incorporated the derivation algorithm for percent predicted FEV1 in section 8.3.2.
0.8	17-Jun-2019		Updated section 7.2 for demographics and baseline characteristics with the inclusion of some more data collected on the CRF for the presentation. Clarified that all the pulmonary exacerbations observed through the end of study will be considered for the primary endpoint analysis. Added subgroup analyses for the primary endpoint and the secondary endpoint related to the rate of pulmonary exacerbation. Added exploratory analyses for all the endpoints specifying that the results will also be presented for the pooled INS1007 treatment group. For the efficacy endpoints, the comparisons will also be done between the pooled INS1007 group and Placebo group. Added sensitivity analysis for the secondary efficacy endpoint of rate of pulmonary exacerbation over the 24-week treatment period. Added the derivation of treatment compliance based on the duration of exposure.

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
0.9	09-Jul-2019	[redacted]	Clarified that the "Visit" variable required for the analyses related to QOL-B and LCQ will be derived based on the chronological occurrence of the assessment and not based on the visits obtained in the vendor data. The changes affected the analyses specified in sections 8.3.1, 8.4.1, 8.4.2, 8.4.10, 8.4.11, and 8.4.14.3 Clarified analyses to be performed for dental evaluation in section 11.7
0.10	21-Oct-2019		Add secondary endpoint with reference to PK SAP. Update WHO DDE and MedDRA dictionary versions. Clarify definition of exacerbation, minimum of 4 weeks is required between one exacerbation and the next. Clarify that derived exacerbations are used for time to first exacerbation analyses. Add category of BQL for Baseline NE in sputum. Update Syneos Health personnel on signature page.
0.11	18-Dec-2019		Update Insmed personnel on signature page. Update MedDRA dictionary version. Update Appendix C based on sponsor's comments.
1.0	09-Jan-2020		Update based on sponsor's comments.

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
[redacted]	10-Jan-2020 Date (dd-Mmm-yyyy)
[redacted]	09-Jan-2020 Date (dd-Mmm-yyyy)
[redacted]	10JAN2020 Date (dd-Mmm-yyyy)
Insmed Incorporated	
[redacted]	10 Jan 2020 Date (dd-Mmm-yyyy)
[redacted]	10 JAN 2020 Date (dd-Mmm-yyyy)

TABLE OF CONTENTS

Contents

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC0-8	Area under the plasma concentration-time curve from 0 to 8 hours
AUC0-24	Area under the plasma concentration-time curve from 0 to 24 hours
BMI	Body Mass index
BP	Blood Pressure
BSI	Bronchiectasis Severity Index
CF	Cystic Fibrosis
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation 1
Cmax	Maximum plasma concentration of drug
Cmax,ss	Maximum plasma concentration at steady state
Cmin,ss	Minimum plasma concentration at steady state
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF/CRF	(electronic) Case Report Form
eGFR	Estimated Glomerular Filtration Rate

Abbreviation	Description
EOS	End of Study
ERS	European Thoracic Society
FDA	Food and Drug Administration
FEF25-75	Forced Expiratory Flow between 25 and 75% of forced vital capacity
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HepC Ab	Hepatitis C Antibody
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IRT	Interactive Response Technology
ITT	Intent-to-treat
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
LCQ	Leicester Cough Questionnaire
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NCFBE	Non-Cystic Fibrosis Bronchiectasis
NCI	National Cancer Institute
NE	Neutrophil Elastase
Pa	Pseudomonas Aeruginosa

Abbreviation	Description
PD	Pharmacodynamic(s)
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
QD	Once daily
QOL	Quality of Life
QOL-B	Quality of Life Questionnaire-Bronchiectasis
SABA	Short-acting Beta Agonist
SAE	Serious Adverse Event
SAMA	Short-acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
T	Body temperature
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listing, and Figure
T_{max}	Time to maximum plasma concentration
$T_{max,ss}$	Time to maximum plasma concentration at steady state
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, data listings, and figures which will be produced, and the statistical methodologies that will be used, are complete, reproducible, and appropriate to allow valid conclusions regarding the study objectives. Analysis of pharmacokinetics (PK), pharmacodynamics (PD), PK-PD and PD-PD analysis will be described in a separate analysis plan.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, listings, and figures (TLFs).

2.2. Timings of Analyses

The primary analysis of safety, efficacy, pharmacokinetics, and pharmacodynamics is planned after all subjects complete the final study visit or terminate early from the study.

Safety analyses specific to Data Monitoring Committee (DMC) will be performed after 25%, 50%, 75% of patients have been randomized, and after the database lock to support DMC meetings approximately 4 to 6 weeks after each database snap shot/lock. The details of the safety analyses will be covered in a separate DMC SAP.

No formal interim analysis is planned during the conduct of this study.

A blinded sample size reassessment is planned for this study. In order to ensure that the study has at least 80% power at the conclusion of the trial, 87 events will need to be observed, regardless of treatment group. Once 70% (n=168) of the randomized subjects on trial have completed study treatment, Insmed anticipates that at least 70% of the required events, or 61 events, will have occurred. The formula for the suggested sample size will be $Y = \frac{61}{x} * 240$ where Y is the new suggested total sample size, x is the observed number of events once 70% (n=168) of the randomized subjects on trial have completed study treatment, 61 is the number of events that was expected to have occurred once 70% of the randomized subjects on trial have completed study treatment, and 240 represents the total number of subjects be randomized based on the original sample size determination. The decision to increase the sample size will be made by the Insmed study team. The sample size will not be decreased based on the sample size reassessment results.

The Insmed study team will be blinded and not aware of either the actual treatment received nor the randomized treatment. No unblinding is necessary to conduct this sample size readjustment. Insmed believes that no type I error correction is necessary to maintain the overall type I error rate (Kieser M et al., 2003).

3. STUDY OBJECTIVES

3.1. Primary Objective

To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation over the 24-week treatment period.

3.2. Secondary Objectives

- To evaluate the effect of INS1007 compared with placebo on quality of life (QOL), as assessed by the Quality of Life Questionnaire-Bronchiectasis (QOL-B), Respiratory Symptoms Domain score, over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on lung function, as measured by forced expiratory volume in 1 second (FEV1), over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the concentration of active neutrophil elastase (NE) in sputum, as measured by the difference between the pre-treatment concentration and on-treatment concentration.
- To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period.

3.3. Exploratory Objectives

- To evaluate the effect of INS1007 compared with placebo on QOL, as assessed by the QOL-B domains (excluding the Respiratory Symptoms Domain) over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on QOL, as assessed by the Leicester Cough Questionnaire (LCQ), over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on respiratory-related health status, as assessed by the St George's Respiratory Questionnaire (SGRQ), over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the concentration of active NE in sputum, as measured by the difference between the pre-treatment concentration and the concentrations at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on the concentration of active NE in reagent-stimulated blood, as measured by the difference between the pre-treatment concentration and the concentrations at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28.

- To evaluate the effect of INS1007 compared with placebo on the concentration of active NE in sputum, stratified by Baseline sputum color, as measured by the difference between the pre-treatment concentration and the concentrations at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on inflammatory and tissue degradation biomarkers in sputum (biomarkers which may be assessed are proteinase 3 and cathepsin G) at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on inflammatory and tissue degradation biomarkers in blood (biomarkers which may be assessed are absolute neutrophil count [ANC], proteinase 3, and cathepsin G) and urine at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on inflammatory and tissue degradation biomarkers in urine (desmosine) at Weeks 2, 4, 12, 24, and 28.
- To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameter as measured by spirometry (forced vital capacity [FVC] over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameter as measured by spirometry (peak expiratory flow rate [PEFR]) over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameter as measured by spirometry (forced expiratory flow [FEF] 25-75% [FEF25-75] over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the total duration of all exacerbations (days per subject) over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on the number of exacerbations per subject over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV1, FVC, PEFR, and FEF25-75), stratified by Baseline Bronchiectasis Severity Index (BSI) score, over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV1, FVC, PEFR, and FEF25-75), stratified by the presence or absence of Pseudomonas aeruginosa (*Pa*) at Screening, over the 24-week treatment period.

- To evaluate the effect of INS1007 compared with placebo on the use of rescue medications (rescue medications include short-acting beta agonists [SABAs], short-acting muscarinic antagonists [SAMAs], newly prescribed long-acting beta agonists [LABAs], long-acting muscarinic antagonists [LAMAs], and oxygen) over the 24-week treatment period.
- To evaluate the effect of INS1007 compared with placebo on hospitalizations for a pulmonary exacerbation over the 24-week treatment period.
- To assess the correlations among inflammatory and tissue degradation biomarkers, concentration of active NE in blood, sputum, and, urine and efficacy measures.

3.4. Safety Objective

To assess the safety and tolerability of INS1007 relative to placebo based on adverse events (AEs), vital sign and ECG measurements, physical exams, pulmonary function tests (PFTs) and clinical laboratory evaluations.

3.5. Pharmacokinetic Objectives

The pharmacokinetic objectives are addressed in a separate PK-PD SAP.

- To evaluate the PK of INS1007.
- To assess the relationship between PK measures for INS1007 and efficacy, safety and biomarker measures (e.g., concentrations of active NE in sputum and reagent-stimulated blood)

3.6. Brief Description

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multi-national study to assess the efficacy, safety and tolerability, and PK of INS1007 administered QD for 24 weeks in subjects with Non-Cystic Fibrosis Bronchiectasis (NCFBE).

This multicenter study will be conducted at approximately 120 sites; enrollment is competitive across all sites. Across these sites, it is planned that approximately 240 subjects with NCFBE will be randomized. Subjects will be randomized in a 1:1:1 ratio to 3 treatment arms (80 /arm) to receive either 10 mg or 25 mg of INS1007 or matching placebo. Randomization will be stratified based on whether the Screening sputum is culture positive for *Pa* and whether the subject is on a maintenance use of macrolides for preventing pulmonary exacerbation.

Each subject will receive study treatment for 24 weeks. The entire study is scheduled to take a maximum of 34 weeks for each individual subject from Screening (Visit 1) to the End of Study (EOS, Visit 10).

A PK sub-study will be conducted at a select number of sites. Subjects who enroll at the selected sites will undergo intensive PK sampling. A maximum of 36 subjects will be included in the PK sub-study. For subjects who participate in the PK sub-study, the visit window for Visit 4 will be ± 5 days. Additionally, for subjects not participating in the PK sub-study, sparse PK sampling will be conducted in subjects at all sites with PK sampling processing capabilities. Pharmacokinetic samples will be analyzed in batches on an ongoing basis.

3.6.1. Screening Period

There will be a screening period of up to 6 weeks per subject. During the screening period, the subject's demographic information, medical history and smoking history will be obtained, a physical exam, vital signs and a sputum sample for sputum culture and active NE concentration will be collected, and chemistry/hematology and urinalysis tests, serum pregnancy test for women of childbearing potential (WOCBP), ECG, PFT, and periodontal cleaning and examination will be conducted. Periodontal examination and dental cleaning procedures for inclusion should be performed prior to randomization.

3.6.2. Treatment Period (Visits 2 through 9)

On Day 1 (Visit 2), vital signs, sputum and blood samples for biomarkers will be collected, and blood chemistry, hematology, and urinalysis tests, ECG, and pregnancy test (WOCBP only) will be conducted. Study sites must confirm subject eligibility based on screening lab results prior to randomization. After re-confirming their eligibility, subjects will be randomized via the Medidata Balance randomization and trial supply management (RTSM) system into 1 of 3 arms to receive either 10 mg or 25 mg of INS1007 or matching placebo in a 1:1:1 ratio.

All eligible subjects will be randomly assigned to treatment, based upon the computer-generated randomization list produced by a Syneos Health independent unblinded biostatistician in consultation with an Insmed in-house statistician. Two randomization lists will be generated, one for the intense PK sub-study and the other for the remaining subjects.

Subjects will receive and be instructed on how to properly use a handheld computer tablet that will be pre-loaded with the QOL-B, LCQ, and SGRQ questionnaires and a dosing diary. Subjects will be required to complete all 3 questionnaires after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). During the duration of the study subjects will complete the 3 questionnaires at the specified times and record their daily dose of study drug in the dosing diary.

Subjects will be provided with a 5-week supply of their assigned study drug at each visit, except Visits 3 and 9. Subjects will be instructed to complete their dosing diary immediately after each dose and return their unused study drug and handheld computer tablet for drug accountability and data entry review at each study visit.

Subjects will be randomized at Visit 2 (Day 1) and return thereafter for study visits at 2, 4, 8, 12, 16, 20, 24 and 28 weeks. There will be a visit window of ± 3 days for each of the scheduled visits.

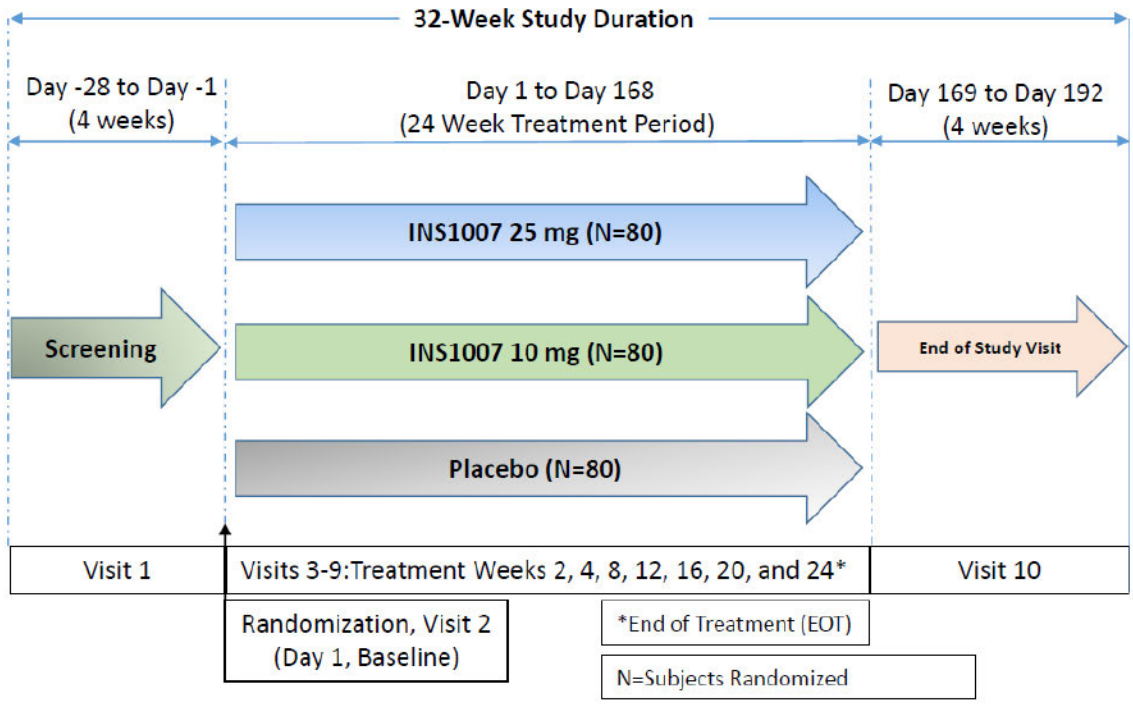
During the treatment period, subjects will be reminded about the importance of birth control and dental hygiene. In addition to the routine safety monitoring, subjects will be closely monitored for hyperkeratosis, periodontitis/gingivitis, and other infections, which will be captured as adverse events of special interest (AESIs) in the study.

3.6.3. End-of-Study Visit (Visit 10)

Subjects will be required to have an EOS visit (Visit 10) at Week 28 to collect blood and sputum samples for biomarker assessment and to collect information on AEs and concomitant medications use. A PK sample will be collected from each subject participating in the PK sub-study.

The study design is illustrated in Figure 1.

Figure 1: Study Design Diagram



3.7. SUBJECT SELECTION

The study will enroll male or female subjects between 18 and 85 years of age at Screening diagnosed with NCFBE (confirmed by chest computed tomography [CT]) who meet all the inclusion and none of the exclusion criteria in the study protocol.

3.7.1. Reasons for Withdrawal/Early Study Discontinuation

Subject early study discontinuation will be summarized based on the following reasons (as provided in the End of Study page of the electronic case report Form [eCRF)]:

1. Death;
2. Adverse event (AE);
3. Protocol violation;
4. Non-compliance with study drug;
5. Subject withdrew consent;
6. Study terminated by Sponsor;

7. Physician decision;
8. Lost to follow up;
9. Pregnancy;
10. Lack of efficacy;
11. Other.

3.7.2. Reasons for Early Treatment Discontinuation

Subject early treatment discontinuation will be summarized based on the following reasons (as provided in the End of Treatment page of the eCRF):

1. Death;
2. AE;
3. Protocol violation;
4. Non-compliance with study drug;
5. Subject decision to withdraw from study treatment;
6. Study terminated by Sponsor;
7. Physician decision to withdraw Subject from study treatment;
8. Lost to follow up;
9. Pregnancy;
10. Treatment code prematurely broken by Investigator
11. Other.

3.8. DETERMINATION OF SAMPLE SIZE

It is expected that pulmonary exacerbations occur at a rate of 1.2 events per subject year in the placebo group, corresponding to 44.6% of the placebo subjects being event free at 24 weeks. It is expected that 40% more event free subjects will be observed within the INS1007 groups (both 10 mg and 25 mg) corresponding to 62.4% of the INS1007 subjects being event free at 24 weeks. The sample size calculation is for the first test in the hierarchical testing procedure. The hazard ratio used in the sample size calculation is $\ln(0.624)/\ln(0.446)=0.584$. Assuming the exacerbation rate in the placebo arm is 1.2 events per subject per year, 216 subjects in total, randomized in a 1:1:1 ratio to 3 treatment arms

with 72 completers per arm, will yield 80% power if the expected difference in the time to the first event is 40% after 24 weeks of treatment with a type I error of 0.1 under a hierarchical testing procedure. Approximately 240 subjects diagnosed with NCFBE will be randomized to provide approximately 216 subjects to complete the study, assuming 10% of the subjects will discontinue study drug before completing 24 weeks of treatment.

The assumed background exacerbation rate from the literature varies from approximately 1 to well above 1 exacerbation per subject per year (Barker et al, 2014; Serisier et al, 2013). Recently published results (DeSoyza et al, 2016) with a similar subject population (2 exacerbations in prior 12 months), showed an exacerbation rate of 1.42 events per subject per year. Based upon these recent results a conservative exacerbation rate of 1.2 was selected, but to ensure sufficient sample size for the study a blinded assessment of the background rate will be performed. If the observed exacerbation rate is smaller than 1.2, the sample size will be reassessed. The decision to increase the sample size will be made by the Insmed study team. The sample size will not be decreased based on the sample size reassessment results.

3.9. TREATMENT ASSIGNMENT & BLINDING

All eligible subjects will be randomly assigned to treatment, based upon the computer-generated randomization list produced by an independent unblinded biostatistician in consultation with an Insmed in-house statistician.

Two randomization lists will be generated, one for the intense PK sub-study and the other for the remaining subjects.

Randomization will be stratified based on the following:

1. Whether Screening sputum is culture positive for *Pa*.
2. Whether the subject is on a maintenance use of macrolides for preventing pulmonary exacerbation.

The randomization will be designed to ensure that the treatment arms are balanced within the intense PK sub-study, sparse PK subjects, and the remaining study subjects. It is expected that most sites will enroll small numbers of subjects, therefore site is not a design parameter for the randomization. The randomization will be global.

3.10. STUDY PROCEDURES AND FLOWCHART

Study schedule of assessments is included in Appendix A: Study Schedule of Assessments

4. ENDPOINTS

The endpoints addressed in this SAP are described in this section.

4.1. PRIMARY ENDPOINT

The primary endpoint is the time to the first pulmonary exacerbation over the 24-week treatment period.

A pulmonary exacerbation in this study is defined as having 3 or more of the following symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics.

1. Increased cough;
2. Increased sputum volume or change in sputum consistency;
3. Increased sputum purulence;
4. Increased breathlessness and/or decreased exercise tolerance;
5. Fatigue and/or malaise;
6. Hemoptysis.

Subjects on chronic macrolide therapy whose only change in therapy is dose or frequency adjustment will not meet the definition of exacerbation.

4.2. SECONDARY ENDPOINTS

1. Change from Baseline in QOL-B respiratory symptoms score over the 24-week treatment period.
2. Change from Screening in post-bronchodilator FEV1 over the 24-week treatment period.
3. Rate of pulmonary exacerbations (number of events per person-time) over the 24-week treatment period.

The endpoints associated with neutrophil elastase in sputum are described in a separate document, PK/PD Statistical Analysis Plan.

4.3. EXPLORATORY ENDPOINTS

1. Change from Baseline in score of QOL-B domains (excluding respiratory symptoms domain) over the 24-week treatment period.

2. Change from Baseline in QOL as assessed by the LCQ score over the 24-week treatment period.

3. Change from Baseline in SGRQ total score over the 24-week treatment period.

4. Change from Baseline in sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28.

5. Change from Screening in FVC at Weeks 12 and 24.

6. Change from Screening in PEFR at Weeks 12 and 24.

7. Change from Screening in FEF_{25-75} at Weeks 12 and 24.

8. Total duration (in days) of exacerbations, per subject, over the 24-week treatment period.

9. Total number of exacerbations per subject over the 24-week treatment period.

10. Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FEV1, FVC, PEFR, and FEF_{25-75}), stratified by Bronchiectasis Severity Index (BSI) score at baseline, over the 24-week treatment period.

11. Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FEV1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pa* at Screening, over the 24-week treatment period.

12. Frequency of use of rescue medications (rescue medications include short-acting beta agonists [SABAs], short-acting muscarinic antagonists [SAMAs], newly prescribed long-acting beta agonists [LABAs], long-acting muscarinic antagonists [LAMAs], and oxygen) over the 24-week treatment period.

13. Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period.

4.4. SAFETY ENDPOINTS

The safety endpoints will include the following:

1. AEs

2. 12-Lead ECG measurements

3. Clinical laboratory testing results

4. Vital sign measurements
5. Physical examination results
6. Pulmonary Function Test (PFT) measurements

AESIs that will be reported include hyperkeratosis, periodontitis/gingivitis, and other infections as identify by the investigator in the case report form.

5. ANALYSIS POPULATIONS

5.1. INTENT-TO-TREAT POPULATION

All subjects who are randomized will be included in the Intent-to-treat (ITT) Population.

Summaries and analyses utilizing the ITT Population will summarize/analyze subjects according to their randomized treatment. The ITT Population will be used for all analyses of efficacy endpoints.

5.2. PER-PROTOCOL POPULATION

All subjects who are randomized and completed the study without any major deviations will be included in the Per-protocol (PP) Population, where subjects with an answer 'Yes' to the question 'Did the Subject complete the study?" given on the eCRF will be considered as completing the study.

Subjects with major deviations will be identified by the Insmed Study team prior to breaking the study blind. Major deviations may include, but are not limited to the following:

1. Subjects did not receive the study treatment to which he/she was randomized
2. Subject did not meet Inclusion Criteria 4 or 7.
3. Subject met Exclusion Criteria 1, 2, 3, 4, 5, 6, 12, 13, 14, 16, 17, 21, or 22.
4. Subject did not complete End of Study Visit (EOS), except for death.

Summaries and analyses utilizing the PP Population will summarize/analyze subjects according to their randomized treatment. The PP population will be used for the supportive analysis of the primary efficacy endpoint.

5.3. SAFETY POPULATION

All subjects who received at least 1 dose of the study drug will be included in the Safety Population.

Summaries and analyses utilizing the Safety Population will summarize/analyze subjects according to their actual treatment received. The Safety Population will be used for all analyses of safety endpoints.

5.4. PHARMACOKINETIC POPULATION

Please see the PK-PD SAP for this definition.

5.5. PHARMACODYNAMIC POPULATION

Please see the PK-PD SAP for this definition.

5.6. PROTOCOL DEVIATIONS

Final assessment of major protocol deviations and assignments of subjects to analysis populations will be discussed in a blind data review meeting prior to the study database lock.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

- SAS® version 9.4 or higher will be used (SAS Institute, Inc, Cary, North Carolina).
- Unless otherwise specified, summaries will be presented for each treatment.
- The total number of subjects in each treatment group (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. A row for summary of missing observations will be included where necessary.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency, and percentages of subjects within the treatment group.
- All subjects will be presented in the subject data listings if information is present and unless otherwise noted.
- In general, the listings will be sorted by treatment (placebo/10 mg INS1007/ 25 mg INS1007, subject number, and assessment date (and time) if applicable.
- Multiple assessments at a given time point (planned, repeat) will not be included in summary tables unless specified otherwise, but will be included in the listings.
- In general, unscheduled visit data will be listed (in date order) but not included in the summary tables.
- Visit labels will be in the format Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, End of Study; all unscheduled visits will have UNS added.

6.2. KEY DEFINITIONS

6.2.1. Baseline

Unless otherwise specified, the baseline assessment will be the last available measurement taken prior to the first dose of study drug.

6.2.2. Nominal Day

Nominal day is the scheduled day relative to first dosing. Day 1 is the day of first dosing. The day immediately prior to dosing is Day -1.

6.2.3. Adverse Events (AEs) and Concomitant Medications (CMs)

A treatment-emergent adverse event (TEAE) is any AE that begins during the treatment-emergent period or the worsening of a pre-existing medical condition during the treatment-emergent period. The treatment-emergent period begins when the subject first receives study drug and ends 30 days after the subject last receives study drug or the date of subject's EOS visit, whichever is later.

AEs that occur between the time the subject signs the ICF for the study and the time when the subject receives his/her first dose will be reported as medical history and not as a TEAE.

Concomitant medications are defined as medications taken after the start of study drug administration or started prior to the start of study drug administration and continued after the start of study drug administration. For AEs/TEAEs and CMs, time since (first) dose will be calculated as the difference between the event or medication start date and the date of the first dose. Time since (first) dose will be expressed in days. Methods for handling partial start dates of AEs and CMs are described in Section 6.3. Duration will be calculated for AEs that resolve as the difference between the start date and end date and will be expressed in days. Time since (first) dose and duration will only be calculated when both dates are complete.

6.3. MISSING DATA

Adverse events and CMs with incomplete start dates will be considered as treatment-emergent or concomitant unless the end date precludes that possibility. The following algorithm will be utilized:

1. If an AE or medication started and stopped prior to the start of study treatment the given AE or medication will be considered as prior. This will be verified using the algorithms below (steps 2 through 3).
2. Only the start year is reported: If the year is after or the same as the year of the first dose date, then the AE will be considered treatment-emergent and the medication will be considered as concomitant unless the end date precludes that possibility.
3. Only the start month and year are reported: If the month/year is after or the same as the month/year of the first dose date, then the AE will be considered treatment-emergent and the medication will be considered as concomitant unless the end date precludes that possibility.

There will be no further imputation of missing data unless otherwise noted.

6.4. VISIT WINDOWS

Data collected at unscheduled visits that occurred outside the time windows specified in the protocol (e.g., post-dose clinical laboratory tests done on days not specified in the protocol) will be included in the data listings but will not be included in the analyses, unless otherwise specified.

6.5. VARIABILITY BY SITE

Given the large number of sites, and a small number of subjects per site, there will be no model adjustment for it.

7. DEMOGRAPHICS, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Listings of treatment assignments, including the randomization number, subject's identification, date of randomization, and treatment group will be presented.

The following frequency of subjects (number and percent) will be displayed by treatment group and across treatment groups: subjects in the Safety population by actual treatment, subjects in the ITT Population by randomized treatment, subjects in the PP Population by randomized treatment, subjects in the PK Population by actual treatment, subjects in the Pharmacodynamic Population by actual treatment, subjects who completed the study by randomized treatment, subjects who discontinued the study early by randomized treatment, the primary reason for early study discontinuation by randomized treatment, subjects who completed the treatment by randomized treatment, subjects who discontinued the treatment early by randomized treatment, and the primary reason for early treatment discontinuation by randomized treatment.

Listings of study and treatment completion/discontinuation, including date of completion/discontinuation, last dose of study drug administration and primary reason for discontinuation will be presented.

All inclusion/exclusion criteria definitions will be listed. Inclusion/exclusion criteria violations will be listed by subject. Protocol deviations will be listed and the major protocol deviations will be identified in the listing.

Subjects excluded from any analysis populations will be listed including the reasons for exclusions.

7.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, including age, sex, race, ethnicity, height, weight, BMI, *Pa* positive, maintenance use of Macrolides, Bronchiectasis Severity Index (BSI), CT Scan confirmation of Bronchiectasis, smoking status, and pack years, three or more exacerbations in prior 12 months, hospitalized for exacerbation in prior 24 months, use of inhaled steroids, FEV1 (% Predicted) < 50%, history of Chronic Obstructive Pulmonary Disease (COPD), and Asthma will be summarized by treatment group and across treatment groups using standard descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum for continuous variables, and the number and percentage of subjects for categorical variables) for all subjects in the ITT, Safety, PP, PD, and PK Populations separately. Patients with medical history of chronic obstructive pulmonary disease, chronic bronchitis, pulmonary emphysema, bronchial obstruction, and bronchitis will be considered as having a history of COPD. No formal statistical comparisons between populations or treatment groups will be performed.

All demographic data and baseline characteristics provided in the tables will also be listed by subject. Information regarding the BSI (the BSI score calculation is described in Appendix B: Calculation of Bronchiectasis Severity Index), CT scan confirmation of Bronchiectasis, and smoking status history will be listed separately for all subjects.

7.3. MEDICAL AND SURGICAL HISTORY

Medical and surgical history will be coded using MedDRA 22.0, sorted alphabetically by system organ class and preferred term, summarized by treatment group and across treatment groups for the Safety Population and ITT Population and listed for all subjects in the ITT Population.

7.4. PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be coded using version Sep 1, 2018 of the World Health Organization drug codes available (WHO DDE); the version used will be documented in a footnote to the listing.

Prior medications are defined as medications with a stop date and time prior to the start of study drug administration.

Prior and concomitant medications will be summarized separately using n (%) of subjects for each treatment group and across treatment groups by ATC class term (ATC4) and standard medication name for the Safety Population. Subjects may have more than one medication per ATC category and standard medication name. At each level of summarization, a subject will only be counted once if one or more medications are reported by the subject at that summary level.

Prior and concomitant medications data will be listed chronologically by treatment group, subject, and will include the data collected in the eCRF, along with the codes. If no prior or concomitant medications are reported, this will be noted in place of the listing.

8. EFFICACY

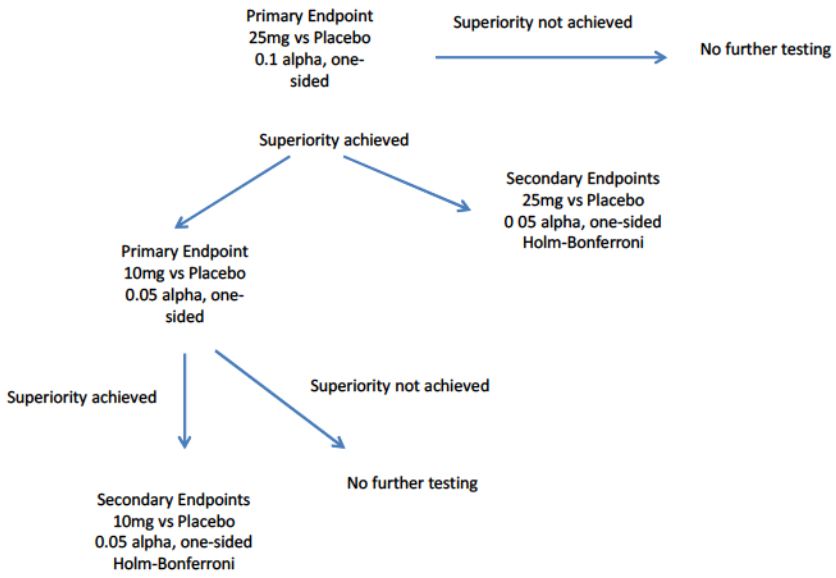
8.1. HIERARCHY OF ENDPOINT TESTING

For all efficacy analyses, INS1007 10mg and 25mg will each be compared separately to placebo. No hypothesis testing between active treatment groups will be conducted. All p-values will be presented as one-sided p-values.

The hierarchy of the analysis is the following: primary analysis of INS1007 25mg against placebo to test the superiority of the INS1007 25mg dose at the one-sided 0.1 alpha level, then the alpha is split between the INS1007 25mg secondary endpoints and the INS1007 10mg primary analysis. If the superiority of INS1007 25mg against placebo is not achieved, then all alpha is spent, and no further hypothesis testing may be conducted.

The secondary endpoints at the INS1007 25mg dose will be tested for superiority against placebo and the type I error rate will be controlled at the one-sided alpha level of 0.05 using the Holm-Bonferroni method. If the primary analysis of INS1007 10mg against placebo does not demonstrate the superiority of the INS1007 10mg dose at the one-sided 0.05 alpha level, then the 0.05 alpha is spent, and no further hypothesis testing will be conducted on the INS1007 10mg secondary endpoints.

If the primary analysis of INS1007 10mg against placebo does demonstrate the superiority of the INS1007 10mg dose at the one-sided 0.05 alpha level, then the 0.05 alpha is not spent and the secondary endpoints at the INS1007 10mg dose will be tested for superiority against placebo and the type I error rate will be controlled at the one-sided alpha level of 0.05 using the Holm-Bonferroni method.



For the exploratory endpoints the p-values will be considered descriptive and hypothesis generating. Type I error will not be controlled for the exploratory endpoints.

8.2. PRIMARY EFFICACY ENDPOINT ANALYSES AND SUMMARIES

8.2.1. The time to the first pulmonary exacerbation over the 24-week treatment period

The primary efficacy analysis will be conducted on the ITT Population. A pulmonary exacerbation in this study is defined as having 3 or more of the following symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics. Such exacerbations will be considered as protocol defined exacerbations.

1. Increased cough;
2. Increased sputum volume or change in sputum consistency;
3. Increased sputum purulence;

4. Increased breathlessness and/or decreased exercise tolerance;
5. Fatigue and/or malaise;
6. Hemoptysis.

Subjects on chronic macrolide therapy whose only change in therapy is dose or frequency adjustment will not meet the definition of exacerbation. This condition will be satisfied if the investigator responds "Y" to "Were new antibiotics prescribed?" on the respective pulmonary exacerbation eCRF page.

A minimum of 4 weeks must occur between one exacerbation onset and the next. Any exacerbations that occur less than 4 weeks from the prior exacerbation will not be considered a new exacerbation.

Any pulmonary exacerbation in the study between Visit 2 through EOS will be included in the primary endpoint, regardless of whether it was associated with a scheduled or unscheduled visit.

The null hypothesis assumes that the time to the first exacerbation is independent of treatment, and the alternative hypothesis assumes that the time to the first exacerbation is associated with INS1007 25mg. The hypothesis will be tested at one-sided alpha of 0.1. Kaplan-Meier product limit estimators of the survivor function (probability of staying event free) will be summarized for medians and their 80% CI, 25th percentiles and 75th percentiles, and the minimum and the maximum.

If the primary analysis of INS1007 25mg against placebo supports the superiority of the INS1007 25mg dose at the one-sided 0.1 alpha level, then the primary analysis of INS1007 10mg against placebo will be test at one-sided alpha of 0.05. Kaplan-Meier product limit estimators of the survivor function will be summarized for medians and their 90% CI, 25th percentiles and 75th percentiles, and the minimum and the maximum.

The time to first pulmonary exacerbation (days) will be calculated as: the time from date of randomization to date of first documentation of exacerbation, as defined above.

The efficacy analysis of the time to the first exacerbation will be performed using the stratified log rank test for the ITT Population and using Kaplan Meier curves. The stratification will be based on the following stratification factors: *Pa* colonization status and maintenance antibiotic use at Baseline (Yes/No) from the randomization.

Subjects who do not have a pulmonary exacerbation during the trial will be censored at the date of last participation in the trial. The number of subjects with an event and censored will be summarized.

Sample SAS® code is shown below:

```
PROC LIFETEST DATA=xxxx METHOD=KM OUTSURV=SURV ALPHAQT=<<0.2 or 0.1>>;
  TIME TTFPE * CNSR (1);
```

```
    STRATA PAERO ANTIBI  / GROUP=TRTP TEST=LOGRANK;
RUN;
```

Where, TTFPE = time to first PE (days), TRTP = randomized treatment group, PAERO = Pa colonization status, ANTIBI = maintenance antibiotic use at Baseline, CNSR(1) = censoring indicator variable where 1 represents censored values.

The plot of Kaplan-Meier estimates for the treatment groups will also be presented.

8.2.2. Sensitivity Analyses of the time to the first pulmonary exacerbation over the 24-week treatment period

The first sensitivity analysis of the primary endpoint, time (in days) to first pulmonary exacerbation is to assess the robustness of the primary analysis to the data scope for the analysis. The primary endpoint will be analyzed in the same manner as the primary analysis, but using the PP Population.

The second sensitivity analysis of the primary endpoint, time (in days) to first pulmonary exacerbation is to assess the impact of the randomization stratification factors. The primary endpoint will be analyzed using the stratified Cox Proportional Hazards model. The model will include the term for treatment group with *Pa* colonization status, and maintenance antibiotic use at Baseline as the stratification factors. It is currently assumed that the proportional hazards assumption will be supported by the data. If the proportional hazards assumption is clearly not supported by the data after observing a statistically significant non-zero correlation between the Schoenfeld residuals and the corresponding ranked failure times, then the proportional hazards results will be deemed invalid due to a violation of the assumptions.

The INS1007 25 mg vs. placebo hazard ratio will be presented with 80% CI. The INS1007 10 mg vs. placebo hazard ratio will be presented with 90% CI. One-sided p-value will be presented for both the treatment group effects.

Sample SAS® code is shown below:

```
PROC PHREG DATA = DATAIN ALPHA=<<0.2 or 0.1>> ATRISK NAMELEN = 70;
CLASS TRTP (REF = 'Placebo') PAERO ANTIBI /ORDER = INTERNAL PARAM = GLM;
MODEL TTFPE*CNSR(1) = TRTP / RISKLIMITS TYPE3 RIDGING = ABSOLUTE;
STRATA PAERO ANTIBI;
LSMEANS TRTP/DIFF;
RUN;
```

Where, TTFPE = time to first PE (days), TRTP = randomized treatment group, PAERO = Pa colonization status, ANTIBI = maintenance antibiotic use at Baseline, CNSR(1) = censoring indicator variable where 1 represents censored values.

The third sensitivity analysis is to assess the robustness of the model to additional covariates. The primary endpoint will be analyzed using the Cox Proportional Hazards

model with treatment group as the main effect and the randomization stratification factors covariates, but also include on-study rescue medication use as a (binary) covariate, where rescue medications include SABAs, SAMAs, newly prescribed LABAs, LAMAs, and oxygen The value of this binary covariate will be considered as "Y" if the patient uses any of the rescue medications while on the study, otherwise it will be considered as "N".

Because the primary efficacy analysis is expected to be highly positively correlated with the sensitivity analyses of the primary endpoint, no alpha adjustments will be made.

8.3. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

8.3.1. Change from Baseline in QOL-B respiratory symptoms score over the 24-week treatment period

The Quality of Life Questionnaire-Bronchiectasis (QOL-B) is a validated, self-administered patient reported outcome (PRO) that assesses symptoms, functioning, and health-related QOL for subjects with NCFBE (Quittner et al, 2014; Quittner et al, 2015). The QOL-B contains 37 items in 8 domains (Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, and Treatment Burden).

The change from Baseline in QOL-B respiratory symptoms score over the 24-week treatment period will be compared between the treatments with a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM) approach.

The model will include the fixed, categorical effects of treatment group, *Pa* colonization status and maintenance antibiotic use at Baseline, visit (based on the chronological order of the completion of the questionnaire), and treatment group-by-visit interaction. Subject will be included in the model as a random effect. An unstructured (co)variance structure will be used to model the within-subject errors. If the convergence is not achieved with an unstructured variance structure then variance component structure will be used. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. The model will be fitted using the SAS®/STAT procedure PROC MIXED, with a RANDOM statement over the visits included and the unique subject identifier as the SUBJECT variable in the RANDOM statement.

Sample SAS® code is shown below:

```
PROC MIXED DATA = DATAIN METHOD = REML;
CLASS TRTP PAERO ANTIBI;
MODEL CHGQOLBR = TRTP VISITN TRTP*VISITN PAERO ANTIBI/ DDFM =
KENWARDROGER;
RANDOM VISITN/SUBJECT = USUBJID TYPE = <UN or VC>;
LSMEANS TRTP/CL PDIFF;
RUN;
```

Where, CHGQOLBR = change from baseline in QOL-B respiratory symptoms score to each post-baseline assessment, TRTP = randomized treatment group, VISITN = visit number (1, 2, 3 etc. based on the chronological occurrence of the assessment), USUBJID = unique subject identifier, PAERO = Pa status, ANTIBI = maintenance antibiotic use at Baseline.

Least squares means (LS means) and mean treatment difference, standard error (SE), 90% CI, 95% CI, and p-value for the treatment effect averaged across the trial, with the same weight applied to each visit, will be presented.

8.3.2. Change from Screening in post-bronchodilator FEV1 over the 24-week treatment period

Post-bronchodilator pulmonary function test by spirometry (FEV1, FVC, PEFR, and FEF25-75) will be performed per the American Thoracic Society (ATS/European Respiratory Society [ERS]) criteria (Miller et al, 2005) at Visit 1 (Screening), Visit 6 (Week 12), and Visit 9 (Week 24).

FEV1 is analyzed using percent predicted FEV (ppFEV1).

Change from Screening in post-bronchodilator ppFEV1 at Visit 6 (Week 12) and Visit 9 (Week 24) separately, will be compared between the treatments with an analysis of covariance with Pa colonization status and maintenance macrolide antibiotic use at Baseline as covariates. The comparison of treatments for change from screening in ppFEV1 at Visit 6 will be considered as hypothesis generating. The LS means and mean treatment difference, SE, 90% CI, 95% CI and p-value for the mean treatment difference will be presented. P-values for the overall treatment effect and 2 covariates will also be presented.

8.3.3. Pulmonary exacerbations over the 24-week treatment period

Pulmonary exacerbation (defined by symptoms, duration of symptoms and antibiotic prescription) will be collected and reviewed throughout the study between randomization through EOS.

Pulmonary exacerbations are defined in Section 8.2.1 .

The rate of pulmonary exacerbation (per person year) over the 24-week treatment period will be calculated for each subject as:

Rate = total number of pulmonary exacerbation / total follow-up duration

Where, total follow-up duration (years) = ([date of EOS – date of randomization] + 1) / 365.25.

Rate will be rounded to two decimal places for displaying purposes.

The number of pulmonary exacerbations over the 24-week treatment period, classified as Yes or No depending on the experience of pulmonary exacerbation by the patient, will be analyzed using Cochran-Mantel-Haenszel statistics for the ITT Population stratified by *Pa* colonization status and maintenance macrolide antibiotic use at Baseline and the corresponding p-value will be presented.

Additional analyses exploring the treatment effect based on the pulmonary exacerbations can be found in Appendix C.

8.4. EXPLORATORY EFFICACY ENDPOINT(S) AND ANALYSES

8.4.1. Change from Baseline in score of QOL-B domains over the 24-week treatment period

The actual and change from Baseline in score of QOL-B domains (excluding respiratory symptoms domain) will be descriptively summarized only for the latest assessment by treatment group. A MMRM model will be fitted as described in section 8.3.1 and the results will be presented in a similar manner.

8.4.2. Change from Baseline in LCQ score over the 24-week treatment period

The Leicester Cough Questionnaire is a validated PRO questionnaire evaluating cough on quality of life in subjects with NCFBE (Murray et al, 2009).

The LCQ comprises 19 items and takes 5 to 10 minutes to complete. Each item assesses symptoms or the impact of symptoms over the last 2 weeks on a seven-point Likert scale. Scores in 3 domains (Physical, Psychological and Social) are calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) is also calculated by adding the domain scores together. Higher scores indicate better QOL.

The actual and change from Baseline in the LCQ domain and total will be descriptively summarized only for the latest assessment by treatment. A MMRM model will be fitted as described in section 8.3.1 and the results will be presented in a similar manner.

8.4.3. Change from Baseline in SGRQ (total) score over the 24-week treatment period

The SGRQ is a self-administered questionnaire that has been validated in subjects with airways disease, specifically in subjects with BR (Jones 1991; Jones, et al. 1991; Wilson, et al. 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)
- Impacts (the effect of disease on factors such as employment, personal control of one's health, and need for medication).

A composite total score is derived as the sum of domain scores for symptoms, activity, and impact, with 0 the best possible score and 100 the worst possible score (Jones P, 2009). Change-from-baseline will be calculated for the SGRQ. A reduction in score of 4 units is generally recognized as a clinically meaningful improvement in quality of life.

No imputation of missing data will be done for the SGRQ. Total scores will not be derived for subjects' with more than 2, 4 or 6 missing items in the symptoms, activity or impacts domains, respectively, nor will the domain score be derived if the number of allowed missing items is exceeded.

The actual and change-from-baseline for total and individual domain scores of the SGRQ will be summarized descriptively by visit and treatment group.

8.4.4. Shift from Baseline in sputum color at Weeks 2, 4, 12, 24, and 28

Shift from Baseline in sputum color (assessed by the sputum color chart) at Visit 3 (Week 2), Visit 4 (Week 4), Visit 6 (Week 12), Visit 9 (Week 24), and Visit 10 (Week 28) will be descriptively summarized by treatment group.

8.4.5. Change from Screening of FVC at Weeks 12 and 24

FVC is described in Section 8.3.28.3.2.

Change from Screening of FVC at Visit 6 (Week 12) and Visit 9 (Week 24) will be descriptively summarized by treatment group.

8.4.6. Change from Screening of PEFR at Weeks 12 and 24

PEFR is described in Section 8.3.2.

Change from Screening of PEFR at Visit 6 (Week 12) and Visit 9 (Week 24) will be descriptively summarized by treatment group.

8.4.7. Change from Screening of FEF25-75 at Weeks 12 and 24

FEF25-75 is described in Section 8.3.2.

Change from Screening of FEF25-75 at Visit 6 (Week 12) and Visit 9 (Week 24) will be descriptively summarized by treatment group.

8.4.8. Total duration of exacerbations, per subject, over the 24-week treatment period

Exacerbations are defined in Section 8.2.1. The total duration (in days) of exacerbations, summed by subject, between Visit 2 (baseline) and EOS will be descriptively summarized by treatment group.

8.4.9. Total number of exacerbations per subject over the 24-week treatment period

Total number of exacerbations over the 24-week treatment period, defined as the duration between Visit 2 and EOS per subject will be descriptively summarized by treatment group.

8.4.10. Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FEV1, FVC, PEFR, and FEF_{25-75}), stratified by Bronchiectasis Severity Index (BSI) score at baseline, over the 24-week treatment period

For the analyses stratified by BSI score at Baseline, the BSI score will be categorized into 3 levels: ≤4, 5-8, and ≥9 points.

Time to first pulmonary exacerbation, as described in section 8.2.1, will be analyzed using stratified log-rank test with BSI score at baseline as a stratification factor and corresponding one-sided p-value will be presented.

The rate of pulmonary exacerbations over the 24-week treatment period, as described in section 8.3.3, will be analyzed using Cochran-Mantel-Haenszel statistics stratified by BSI score at baseline and the corresponding p-value will be presented.

Observed and change from baseline in QOL-B scores (all the domains) will be descriptively summarized only for the latest assessment for all the treatment groups by stratified BSI score at baseline.

Observed and change from screening in pulmonary function parameters (FEV1, FVC, PEFR, and FEF_{25-75}) will be descriptively summarized for all treatment groups for all the available visits by stratified BSI score at baseline.

8.4.11. Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FEV1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pa* at Screening, over the 24-week treatment period

All the analyses mentioned in section 8.4.10 will be repeated by replacing stratified BSI score with the categorical variable representing presence or absence of Pa at Screening.

8.4.12. Frequency of use of rescue medications over the 24-week treatment period

The frequency of rescue medications use between Visit 2 (baseline) and Visit 9 (Week 24) will be calculated per subject and descriptively summarized by treatment group. Rescue medications include SABAs, SAMAs, newly prescribed LABAs, LAMAs, and oxygen.

8.4.13. Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period

The number of subjects hospitalized due to pulmonary exacerbations between Visit 2 (baseline) and the date of EOS will be tabulated by treatment group and across treatment

groups. In addition, the total number of days a subject spent in the hospital due to pulmonary exacerbations will also be summarized by treatment group.

The number of subjects admitted to the ICU due to pulmonary exacerbations between Visit 2 (baseline) and the date of EOS will be tabulated by treatment group and across treatment groups. In addition, the total number of days a subject spent in the ICU due to pulmonary exacerbations will also be summarized by treatment group.

8.4.14. Other exploratory analyses

8.4.14.1. Pooled INS1007 Analyses

All the p-values will be presented as one-sided p-values. These analyses will be termed as exploratory and no formal alpha adjustment will be performed. The sensitivity analyses performed for the individual efficacy endpoints will not be performed for the pooled INS1007 vs. Placebo comparisons.

8.4.14.2. Subgroup Analyses of the time to the first pulmonary exacerbation and the rate of pulmonary exacerbation

A subgroup analysis of time to first pulmonary exacerbation will be done using the stratified and un-stratified Cox Proportional Hazards. The INS1007 25 mg vs. Placebo hazard ratio will be presented with 2-sided 80% CIs and INS1007 10 mg vs. Placebo hazard ratio will be presented with 2-sided 90% CIs.

A subgroup analysis of rate of pulmonary exacerbation (INS1007 10 mg or 25 mg vs. Placebo) using a negative binomial regression method as described earlier in section 8.3.3 will be performed. The rate ratio and 2-sided 90% CIs will be provided for the comparison of INS1007 10 mg or 25 mg vs. Placebo.

Following subgroups will be explored:

- Age: ≥ 65 years, < 65 years, ≥ 75 years (geriatric), < 75 years (Non-geriatric)
- Pulmonary exacerbations (Baseline variable): 0-2, ≥ 3
- Maintenance use of macrolides at Baseline: Yes, No
- Pa colonization status: Yes, No
- Serious pulmonary exacerbation: Yes, No
- Baseline NE in sputum: ≥ 20 µg/mL, LLOQ to < 20 µg/mL, BQL
- Baseline BSI score: ≥ 5, < 5
- Baseline FEV1 % Predicted: < 50%, ≥ 50%
- Geographical region: Europe, North America, Asia-pacific, Eastern Europe (Bulgaria/Poland)

8.4.14.3. Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FVC, PEFR, and FEF_{25-75}), stratified by ppFEV1 result at baseline, over the 24-week treatment period

For the analyses stratified by ppFEV1 result at Baseline, the ppFEV1 result will be categorized into 2 levels: $< 50\%$ and $\geq 50\%$.

Time to first pulmonary exacerbation, as described in section 8.2.1, will be analyzed using stratified log-rank test with ppFEV1 categories at baseline as a stratification factor and corresponding one-sided p-value will be presented.

The rate of pulmonary exacerbations over the 24-week treatment period, as described in section 8.3.3, will be analyzed using Cochran-Mantel-Haenszel statistics stratified by ppFEV1 categories at baseline and the corresponding p-value will be presented.

Observed and change from baseline in QOL-B scores (all the domains) will be descriptively summarized only for the latest assessment for all the treatment groups by stratified ppFEV1 result at baseline.

Observed and change from screening in pulmonary function parameters (FVC, PEFR, and FEF_{25-75}) will be descriptively summarized for all treatment groups for all the available visits by stratified ppFEV1 result at baseline.

9. ANALYSIS OF PHARMACOKINETICS

Analyses of pharmacokinetics as well as PK-PD analysis will be described in the PK-PD SAP.

10. ANALYSIS OF PHARMACODYNAMICS

Analyses of pharmacodynamics as well as PD-PD analysis will be described in the PK-PD SAP.

11. SAFETY

The population used for safety analyses will be the Safety Population.

11.1. DURATION OF EXPOSURE

Summary statistics will be provided for the duration of exposure (number of days) of study drug (last known date patient took study drug - first dose date + 1) by treatment group.

Treatment administration as collected in the eCRF will be listed chronologically by treatment group and subject.

11.2. TREATMENT COMPLIANCE

The percentage of subjects taking < 80%, 80% - 125%, and > 125% of the intended quantity of the study drugs will be summarized by treatment group, where intended quantity is 168 tablets (1 tablet per day x 7 days per week x 24 weeks of treatment).

Treatment compliance will also be calculated based on the duration of exposure as follows:

Treatment compliance through end of treatment (%) = (number of actual tablets taken / [1 tablet per day x duration of exposure]) *100.

11.3. ADVERSE EVENTS

Adverse events will be coded using MedDRA (version 22) system organ class and preferred term. The severity of AEs will be graded per the NCI CTCAE v4.0.

If a subject has an AE with unknown severity grade, then the AE will be assumed to be of grade 3 severity. If the relationship to study drug is missing and the AE started on or after the first dose of study drug, it will be assumed to be "Definitely Related" to study drug. If the relationship to study drug is missing and the AE began prior to the first dose of study drug, it will be assumed to be "Not Related" to study drug. If the relationship to study drug is missing and the AE began more than 30 days after the last dose of study drug, it will be assumed to be "Not Related" to study drug.

All TEAEs will be summarized by SOC and PT by the number and percentage of subjects experiencing at least one occurrence of the event by treatment group, pooled INS1007 group and across treatment groups. The denominator in the calculation of all TEAE percentages will be the number of subjects in the Safety Population for the given treatment group.

All AEs will be listed by treatment group, patient, and then chronologically by date and time of onset. This listing will include all data collected in the eCRF, along with the derived variables: time since first dose, duration, and the coded variables.

11.3.1. Summaries of Treatment-emergent Adverse Events

Incidence tables presenting the frequency and percent of AEs by SOC and PT will be ordered alphabetically by SOC and then, within a SOC, by overall descending frequency of PT. Subjects will be counted only once within each SOC and PT reporting level on the tables. The tables will present the number of subjects with percentage, and the total number of events per category.

An overview of all TEAEs, serious TEAEs, and TEAEs of Special Interest will present the number and percentage of subjects in the following categories:

- Any TEAE
  - Maximum severity: Mild
  - Maximum severity: Moderate
  - Maximum severity: Severe
  - Maximum severity: Life threatening
  - Maximum severity: Death
- CTCAE grade 3 or higher
- At least one related TEAE
- At least one serious TEAE
- Subjects discontinued study due to a TEAE
- Subjects discontinued treatment due to TEAE
- Died on study due to TEAE

Subjects will be counted once in each of the above categories except for maximum severity. Subjects will be counted only once at the highest severity reported. For example, if a subject has a mild and severe headache and a moderate rash, the subject will be counted under maximum severity of severe only.

Treatment-emergent adverse event tables will present the data by treatment group and across all treatment groups. Incidence tables will be created for the following groups of TEAEs:

- All TEAEs
- Study drug related TEAEs
- TEAEs leading to study withdrawal
- Study drug related TEAEs leading to study withdrawal
- All TEAEs by severity
- All TEAEs by relationship to study drug
- All serious TEAEs
- Study treatment related serious TEAEs
- Serious TEAEs leading to study withdrawal
- Study treatment related serious TEAEs leading to study withdrawal
- Serious TEAEs resulting in death

- Study treatment related serious TEAEs resulting in death
- All non-serious TEAEs
- All TEAEs of special interest
- All serious TEAEs of special interest
- Study treatment related TEAEs of special interest
- TEAEs of special interest leading to study withdrawal
- Study treatment related TEAEs of special interest leading to study withdrawal
- TEAEs of special interest resulting in death
- Study treatment related TEAEs of special interest resulting in death

Study treatment related AEs are AEs that are defined as possibly, probably or definitely related to study treatment.

The following AEs will be summarized by PT for each treatment group and overall.

- TEAEs
- Serious TEAEs
- Common (>5% in any treatment) Non-serious TEAEs

These tables will be sorted in the descending frequency of PT across all treatment groups.

If there are no AEs to report on any of the above tables, the table should be created with the line 'No adverse events were reported' in the body of the table. AEs, AEs leading to death, serious AEs, AEs leading to study discontinuation, and AEs of special interest will be listed separately.

11.4. CLINICAL LABORATORY EVALUATIONS

11.4.1. Tests

Clinical laboratory tests include:

Hematology: Red Blood Cell (RBC) count, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean cell hemoglobin, Mean corpuscular hemoglobin concentration, Complete Blood Count (CBC) with differential, Platelet count.

Blood Chemistry: Sodium, Potassium, Calcium, Chloride, Blood urea nitrogen, Creatinine, Glucose, Total protein, Albumin, Alkaline phosphatase, Creatinine kinase, Total bilirubin, Aspartate aminotransferase/glutamic oxaloacetic transaminase, Alanine aminotransferase, Uric acid, lactate dehydrogenase (LDH), Cholesterol, Triglycerides, Serum bicarbonate.

Urinalysis: pH, Specific gravity, Protein, Glucose, Ketone, Hemoglobin, Bilirubin, Urobilinogen, Nitrite, Leucocytes, Urine Protein and creatinine quantification and ratio calculation, U-Protein, U-Creatinine (Urine protein and creatinine quantification and ratio

calculation will only be performed when a subject is suspected to have renal injury per PI discretion).

Special Tests: HIV, Hepatitis B surface antigen, hepatitis C antibody, serum pregnancy tests, C-reactive protein, and prothrombin time.

11.4.2. Derived and Imputed Data

Clinical laboratory test results will be assigned a Low/Normal/High (LNH) classification by the central laboratory according to whether the value is below (L: low), within (N: normal), or above (H: high) the laboratory parameter's normal range; categorical laboratory test results will be classified as normal (N) or abnormal (A).

Some numeric lab values may be reported as '<n.n' or '>n.n'; these will be analyzed in the summary statistics as n.n/2 and n.n respectively. For example, triglycerides recorded as <0.50 mmol/L would be summarized as 0.25 mmol/L and potassium recorded as >9.0 mmol/L would be summarized as 9.0 mmol/L.

11.4.3. Data Summarization and Presentation

C-reactive protein, erythrocyte sediment rate, serum pregnancy test, prothrombin time, and serology will be listed. Assays which are only measured if other assays are abnormal (e.g., microscopy) will be listed, but not summarized.

Standard descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and changes from baseline will be tabulated by clinical laboratory parameter and visit, for continuous laboratory parameters. The data will be summarized by treatment group and pooled INS1007 group

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

Mean profiles for each clinical laboratory parameter will be generated with data plotted against time by treatment group.

Clinical laboratory sample data and values from clinical laboratory assessments will be listed chronologically by treatment group, subject, and visit.

No inferential tests will be conducted on lab data.

11.5. VITAL SIGNS

11.5.1. Measurements

Vital signs will consist of systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiration rate (breaths/min), and temperature (°C).

11.5.2. Data Summarization and Presentation

Vital signs data (absolute values, change from baseline values, and percentage change from baseline values) will be summarized for each parameter and visit by treatment group and pooled INS1007 group. Mean profiles for each vital signs parameter will be generated with data plotted against time by treatment group. Vital signs will be listed chronologically by treatment group, subject, and visit.

11.6. ECG

11.6.1. Measurements

A 12-lead ECG will be performed.

11.6.2. Data Summarization and Presentation

ECG data (interpretation: Normal; Abnormal – not clinically significant; Abnormal – clinically significant) will be tabulated for each parameter and visit by treatment group and pooled INS1007 group. ECG data will be listed chronologically by treatment group, subject, and visit.

11.7. DENTAL EVALUATION

Oral and dental inspection will be performed by the Investigator at each visit. If there are any signs or symptoms of oral infection, gingivitis, or periodontitis or deterioration of the preexisting conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to the study designated dentist for further assessment. The oral and dental evaluation by the dentist for the subject should then be assessed thereafter on an interval per the dentist discretion until end of the study.

Dental evaluation in terms of tooth status and the ranges for Pocket depth, Cemento-enamal junction, Audio lingual and Gingival inflammation as performed by the designated dentist will be listed chronologically by treatment group, subject, and visit for upper and lower teeth.

Pocket depth will be summarized by visit by category (1-15) and n (number of observations) mean, SD, SE, 95% CI, and change from baseline by category (-15… +15) and n (number of observations) mean, SD, SE, 95% CI. Gingival Inflammation will be presented by treatment and visit. Summary of Subjects with changes from Baseline of 2 mm and more in Pocket Depth in 3 or more areas will be presented by Treatment by post-baseline visit (Week

8 and Week 24). Subjects with changes of 2 mm and more in Pocket Depth in ≥ 3 areas will be listed separately.

12. INTERIM ANALYSES

No formal interim analysis will be performed.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes from the analyses planned in the protocol.

14. REFERENCE LIST

Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, et al. Aztreonam for inhalation solution in subjects with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med. 2014;2(9):738-49.

Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576-85.

DeSoyza A, Aksamit T, Bandel TJ, Criollo M, Elborn JS, Krahn U, et al. Efficacy and Tolerability of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in Bronchiectasis (Non-CF Etiology): Results from the Phase III RESPIRE 1 Study. Chest. 2016;150(4_S):1315A. doi: 10.1016/j.chest.2016.08.1446.

Jones P; St George Respiratory Questionnaire Manual version 2.3, June 2009, Division of Cardiac and Vascular Science at St George's, University of London, UK.

Kieser M, Friede T. The Simple procedures for blinded sample size adjustment that do not affect type I error rate. Statistics in Medicine, 2003

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al; ATS/ERS Task Force. Standardization of spirometry. Eur Respir J. 2005;26(2):319-38.

Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(2):361-4.

Murray MP, Turnbull K, MacQuarrie S, Pentland JL, Hill AT. Validation of Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31.

Quittner AL, Marciel KK, Salathe MA, O'Donnell AE, Gotfried MH, Ilowite JS, et al. A preliminary quality of life questionnaire – bronchiectasis: a patient-reported outcome measure for bronchiectasis. Chest. 2014;146(2):437-48. doi:10.1378/chest.13-1891.

Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, et al. Quality of Life Questionnaire – Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015 Jan;70(1):12-20. doi:10.1136/thoraxjnl-2014-205918. Epub 2014 Oct 16.

Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA. 2013;309(12):1260-7.

15. PROGRAMMING CONSIDERATIONS

Computer-generated table, listing and figure output will adhere to the following specifications.

15.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format. In addition, a compiled file containing all TLFs will be generated.
- Numbering of TFLs will follow ICH E3 guidance.

15.2. TABLE, LISTING, AND FIGURE FORMAT

15.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output should have the following header at the top left of each page:

  Insmed Incorporated Protocol INS1007-201
  (Syneos Health Study Number 1009113)

- Draft/Final (with version number) All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- All output should have CONFIDENTIAL in the top center of each page.
- The date and time output was generated should appear along with the program name, location, and datasets used as a footer on each page.

15.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Population

15.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis population.

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and

- numbers containing fractional portions are decimal aligned.

15.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median and quartiles for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (SD)	XXX.X (X.XX)
Median	XXX.X
Min, Max	XXX, XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis population for the treatment group

who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatments (placebo/ 10 mg INS1007/ 25 mg INS1007), patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

15.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g.,mean change from Baseline) values will be displayed on the Y-axis.

15.2.5.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Patient specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, listing, or figure. If more than 6 lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source, if applicable (i.e., 'Data Source: ADXX, Corresponding Listing xxxx Program: xxxx.sas Table Generation: ddmmmyyyy or 'Program: xxxx.sas Listing Generation: ddmmmyyyy'), as well as the location of the program and the datasets used.

15.3. DERIVATION OF ONE-SIDED P-VALUE

The one-sided p-value for a superiority test is either P/2 or 1-(P/2), where P is a two-sided p-value reported by the given SAS procedure.

If the estimated statistic (e.g. hazard ratio, LS mean difference etc.) is in favor of the alternative hypothesis (i.e. INS1007 is better than Placebo) then the one-sided p-value will be derived as (P/2).

If the estimated statistic is in the opposite direction of the alternative hypothesis (i.e. Placebo is better than INS1007), then the one-sided p-value will be derived as [1 - (P/2)].

16. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. All SAS programs are checked for logic by the developer and verifier, if applicable.

Changes to a program performed after the first release date (i.e., delivery to the sponsor) are documented in the header of the program as change history (documented together with date, reason for change and the name of the programmer who made the changes).

All programs for production of SDTM data sets, analysis data sets and TLFs are double programmed by the verifier. Initial programming results and verification programming results are compared electronically. Tables and listings are double programmed and results of the initial programming and the verification programming are compared electronically. The verification process for figures may follow the double-programming process, or by confirming that data points contained in the plot are consistent against a source table or listing.

17. MOCK-UPS

Attachment: INS1007-201 TLF shells draft v10.docx

18. APPENDICES

APPENDIX A: STUDY SCHEDULE OF ASSESSMENTS

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -28 to -1	Day 1 (Baseline)	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 141 Week 20	Day169 Week 24 (EOT)	Day 197 Week 28
	Visit 1	Visit 2	Visit 3 (± 3 days)	Visit 4 (± 3 days)	Visit 5 (± 3 days)	Visit 6 (± 3 days)	Visit 7 (± 3 days)	Visit 8 (± 3 days)	Visit 9 (± 3 days)	Visit 10 (± 3 days)
Obtain Informed Consent	X									
Demographics and Medical History	X									
Smoking Status	X	X	X	X	X	X	X	X	X	X
Height, Weight, and BMI Calculation	X								X[a]	
Vital Signs (BP, HR, T, RR)	X	X	X	X	X	X	X	X	X	X
Physical Examination	X					X			X	X
Pulmonary Function Test by Spirometry	X					X			X	
Chest CT Scan (if subject does not have prior radiological confirmation of bronchiectasis diagnosis)	X									
12-lead ECG	X	X	X	X	X		X		X	
Special laboratory tests (C-reactive protein, prothrombin time)	X	X	X	X	X	X	X	X	X	X

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -28 to -1	Day 1 (Baseline)	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 141 Week 20	Day169 Week 24 (EOT)	Day 197 Week 28
	Visit 1	Visit 2	Visit 3 (± 3 days)	Visit 4 (± 3 days)	Visit 5 (± 3 days)	Visit 6 (± 3 days)	Visit 7 (± 3 days)	Visit 8 (± 3 days)	Visit 9 (± 3 days)	Visit 10 (± 3 days)
Clinical Laboratory Tests (Hematology, Blood Chemistry and Urinalysis) [b]	X	X[c]	X	X	X	X	X	X	X	X
HBsAg, HIV, and HepC Ab Tests	X									
Serum Pregnancy Test[d]	X									
Estimated Glomerular Filtration Rate Calculation per CKD-EPI Formula	X								X	
Sputum Sample Collection for Sputum Color Determination and Evaluating NE and Other Biomarkers[e]	X	X	X	X		X			X	X
Sputum Microbiology Culture for Pseudomonas and Result Review[f]	X								X	
Dental Examination[g]	X				X				X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Randomization[h]		X								
Urine Pregnancy Test[d]		X		X	X	X	X	X	X	X

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -28 to -1	Day 1 (Baseline)	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 141 Week 20	Day169 Week 24 (EOT)	Day 197 Week 28
	Visit 1	Visit 2	Visit 3 (± 3 days)	Visit 4 (± 3 days)	Visit 5 (± 3 days)	Visit 6 (± 3 days)	Visit 7 (± 3 days)	Visit 8 (± 3 days)	Visit 9 (± 3 days)	Visit 10 (± 3 days)
MRC Breathlessness Scale Assessment and Bronchiectasis Severity Index Calculation		X								
SGRQ Completion and Review[i]		X				X			X	
QOL-B Completion and Review[i]		X	X	X	X	X	X	X	X	
LCQ Completion and Review[i]		X	X	X	X	X	X	X	X	
Blood and Urine Sample Collection for Evaluating NE and Other Biomarkers		X[c]	X	X		X			X	X
PK Sampling for INS1007[j]		X Intense PK Sampling	X Intense PK Trough Sampling	X Sparse PK and Intense PK Sampling		X Sparse PK and Intense PK Trough Sampling			X Sparse PK and Intense PK Trough Sampling	X Intense PK Trough Sampling
Study Drug Dispense, Accountability of Returned Drug, and Review of Dosing Diary		X	X[n]	X	X	X	X	X	X[n]	

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -28 to -1	Day 1 (Baseline)	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 141 Week 20	Day169 Week 24 (EOT)	Day 197 Week 28
	Visit 1	Visit 2	Visit 3 (± 3 days)	Visit 4 (± 3 days)	Visit 5 (± 3 days)	Visit 6 (± 3 days)	Visit 7 (± 3 days)	Visit 8 (± 3 days)	Visit 9 (± 3 days)	Visit 10 (± 3 days)
Pulmonary exacerbation Symptom Entry and Review		X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Dental Hygiene Education[k]		X	X	X	X	X	X	X		
Assessment of Oral Infection, Gingivitis, Periodontitis, and Skin Conditions (especially hyperkeratosis or erythema of palms and soles)[l]			X	X	X	X	X	X	X	X
Child–Pugh Score (only for subjects whose liver function tests are abnormal and suspected to have chronic liver disease to assess for eligibility)[m]	X									
Urine Protein and Creatinine Quantitative Test and Ratio Calculation[m]			X	X	X	X	X	X	X	X

[a] Weight only.

[b] Clinical laboratory blood samples should be collected in a fasted state (after an overnight fast for morning sample collection or at least 4 hours without food at other times) if possible. Urinalysis will be performed using dipsticks with clean catch urine samples.

[c] Vital Signs and clinical laboratory blood samples should be collected prior to the first dose of the study drug on Day 1.

[d] Serum and urine pregnancy tests will be performed for females of child-bearing potential only.

[e] Subjects will be required to provide a sputum sample during the specified visits. A subject may not undergo a sputum induction procedure during Screening (Visit 1) to meet eligibility. On Day 1, the sputum sample should be collected prior to the first dosing of the study drugs. If a subject is unable to provide a spontaneous sputum sample during any visit, chest physiotherapy should be performed first to facilitate expectoration. If chest physiotherapy fails, the recommended sputum induction procedure detailed in the protocol should be performed to obtain a sputum sample.

[f] Sputum microbiology culture for *Pseudomonas* will be performed with the sputum sample obtained at Screening. The result will be reviewed at Baseline and used for randomization stratification.

[g] All subjects need a dental exam. If a subject states that he/she has no teeth, a dentist should confirm that the subject has no teeth and/or implants supporting a denture. Any denture sores or any other pathology should be noted but will not exclude the subject from the study. . . All other subjects who meet all inclusion and exclusion criteria are required to have a dental examination that includes a full-mouth dental radiography and oral examination to evaluate the conditions of oral soft tissue, gingiva, and teeth during Screening. Subjects who are considered a screen failure for reasons not related to the dental exclusion criteria (exclusion criteria 29 through 32) do not need to repeat the dental examination if they are re-screened within 3 months of the first Screening visit. Subjects who have the images of a full-mouth dental radiography that are performed within 6 months of Screening and available for review are not required to have another dental radiography done during Screening. Subjects who are eligible for the study will have a dental deep cleaning (scaling and root planing) before randomization. The evaluation and recording of oral and dental conditions are detailed in the study protocol. The dental examination for Visits 5 and 9 can be performed ± 7 days of the visit date.

[h] Eligibility should be reassessed prior to randomization at Visit 2 (Baseline). Subjects who do not meet all inclusion/exclusion criteria will NOT be randomized and will be considered a screen failure. Subjects who failed at Screening can be re-screened up to 2 times upon Sponsor approval.

[i] Subjects will complete the SGRQ every 12 weeks and the QOL-B and LCQ every 2 weeks until Visit 10. Subjects will be required to complete all 3 questionnaires after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1).The subjects will complete the questionnaires while they are in the clinic at each of the study visits and at home for the weeks in between the study visits. The completed questionnaires should be reviewed during each visit. Subjects will be retrained on how to complete the questionnaires correctly if needed.

[j] For the 36 subjects who participate in the PK sub-study, the PK samples will be collected through an indwelling catheter into vacutainers with K_2EDTA prior to the first dose of the study drugs in the morning on Day 1 and at 1, 2, 3, 4, 6, 8 hours postdose, and prior to the morning dose during Visit 4 and at 1, 2, 3, 4, 6, 8 hours postdose on that visit day; a collection time window of ±10 minutes will be permitted at each time point. In addition, a trough PK sample (predose of INS1007) will be collected at Visits 3, 6, 9 and 10. For subjects who participate in the PK sub-study, the Visit 4 window will be ± 5 days.

For the subjects who are enrolled at sites having PK sample processing capability but not participating in the intensive PK sub-study, 1 PK sample each will be collected (either pre- or postdosing on the visit day) at 3 visits of Visits 4, 6, and 9, respectively. For subjects participating in the intensive PK sub study, a meal will be given after the 1-hour blood draw at Visits 2 and 4 (refer to Appendix 4 for blood sampling times).

[k] Dental hygiene education includes daily teeth brushing and flossing.

[l] Oral and dental inspection will be performed by the Investigator at each visit. If there are any signs or symptoms of oral infection, gingivitis, or periodontitis or deterioration of the preexisting conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to the study designated dentist for further assessment. The oral and dental evaluation by the dentist for the subject should then be assessed thereafter on an interval per the dentist discretion until end of the study.

Skin examination, especially palms and soles, dorsum of the hands and feet, Achilles tendon area, knees, and elbows, will be performed by the Investigator at each visit. If there are any signs or symptoms of hyperkeratosis or erythema or deterioration of the preexisting conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to a dermatologist for further assessment. The skin evaluation by the dermatologist for the subject should then be assessed thereafter on an interval per the dermatologist discretion until end of the study.

[m] Urine protein and creatinine quantification and ratio calculation will be performed only when a subject is suspected to have renal injury per Investigator discretion.

[n] No study drug dispensing at this Visit

BP = blood pressure; BMI = body mass index; CKD-EPI = chronic kidney disease epidemiology collaboration equation 1; CT = computerized tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HepC Ab = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LCQ = Leicester Cough Questionnaire; MRC = Medical Research Council; NE = neutrophil elastase; PK = pharmacokinetic(s); QOL-B = Quality of Life Questionnaire-Bronchiectasis; SGRQ = St George's Respiratory Questionnaire; T = body temperature.

APPENDIX B: CALCULATION OF BRONCHIECTASIS SEVERITY INDEX

Severity Criteria	0 Point	1 Point	2 Point	3 Point	4 Point	5 Point	6 Point
Age (Years)	< 50	-	50 to 69	-	70 to 79	-	80+
BMI (kg/m^2)	> 18.5	-	< 18.5	-	-	-	-
FEV_1 (% Predicted)	> 80%	50 to 80%	30 to 49%	< 30%	-	-	-
Hospital Admissions in the Past 2 Years	No	-	-	-	-	Yes	-
Exacerbation Frequency in Last 12 Months	0 to 2	-	3 or More	-	-	-	-
MRC Dyspnea Score	1-3	-	4	5	-	-	-
Colonization Status	Not Colonized	Chronic Colonization	-	*Pa* Colonization	-	-	-
Radiological Severity	< 3 Lobes Involved	3 or More Lobes or Cystic Changes					

Note: Estimated outcomes are those observed across 5 European treatments in the original derivation and validation study (Chalmers JD et al, 2014).
BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, MRC = Medical Research Council; *Pa* = *Pseudomonas aeruginosa*.

APPENDIX C: EXPLORATORY STATISTICAL ANALYSIS PLAN

Note: The exploratory analyses as described in this appendix will be performed by Insmed. Inc.

Sponsor Name:	**Insmed Incorporated**
Protocol Number and Title:	**INS1007-201 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis - The Willow Study**
Original Protocol:	**21 June 2017**
Protocol Amendment numbers and dates	**Amendment 1.0, 24 August 2017** **Amendment 2.0, 12 March 2018** **Amendment 3.0, 27 April 2018** **Amendment 4.0, 24 September 2018**
Author:	[redacted]
ESAP Version:	1.0
ESAP Version Date:	20 December 2019

1. Introduction

The objective of this Exploratory SAP is to outline several exploratory analyses that assess the rate of exacerbation as evidence of efficacy of INS1007 vs. placebo.

2. Totality of evidence

2.1. The Rate of exacerbations

The purpose of this exploratory analysis SAP is to outline how the rate of exacerbations the analysis on will be analyzed. The possibility that INS1007 is more effective in certain sub-populations will be investigated. The strength of evidence will not necessarily depend on any p-values.

3. Analysis populations

The analysis populations will include the ITT population.

3.1. Sub-population of clinical relevance

A subgroup analysis of rate of pulmonary exacerbation (INS1007 10 mg or 25 mg vs. Placebo) using a negative binomial regression method as described earlier in section 8.3.3 will be performed. The rate ratio and 2-sided 90% CIs will be provided for the comparison of INS1007 10 mg or 25 mg vs. Placebo.

Following subgroups will be explored:

- Age: ≥ 65 years, < 65 years, ≥ 75 years (geriatric), < 75 years (Non-geriatric)
- Pulmonary exacerbations (Baseline variable): 0-2, ≥ 3
- Maintenance use of macrolides at Baseline: Yes, No
- Pa colonization status: Yes, No
- Serious pulmonary exacerbation: Yes, No
- Baseline BSI score: ≥ 5, < 5
- Baseline FEV1 % Predicted: < 50%, ≥ 50%
- Geographical region: Europe, North America, Asia-pacific, Eastern Europe (Bulgaria/Poland)
- Neutrophil elastase in sputum at baseline 2 categories (<20, ≥20)

- Oral steroids at baseline Yes or No
- Inhaled steroids at baseline Yes or No

4. Statistical analysis

4.1. General statistics

Point estimates and 90% confidence intervals will be calculated and summarized.

4.2. Modeling for the rate of exacerbation

The rate of exacerbation will be analyzed with both negative binomial distribution test and the Anderson – Gill model test.

4.1.1. Negative binomial model

Negative binomial models can be estimated in SAS using proc genmod. The type3 option is used to get the multi-degree-of-freedom test of the categorical variables listed on the class statement, and the dist = negbin option is used to indicate that a negative binomial distribution should be used.

Negative binomial model:

```
proc genmod data=nb;
    class trt01an (REF = '1') MACROUSE SPUTUCUT;
    model PEXNUM=trt01an MACROUSE SPUTUCUT /type3 dist=NB link=log
offset=logyrs;
    estimate "25 mg vs Placebo rate ratio" trt01an  1 0 0 /alpha=0.05
exp;
    estimate "10 mg vs Placebo rate ratio" trt01an  0 1 0 /alpha=0.05
exp;

    lsmeans trt01an /cl diff exp;

run;
```

Where, trt01an = treatment group (INS1007 10 mg or 25 mg vs. Placebo), PEXNUM = Number of pulmonary exacerbations, logyrs = Logarithm of Treatment Duration in Years.

4.1.2. Anderson-Gill model -data preparation

As a patient can have recurrent exacerbations, there will be additional sensitivity analysis; The analysis will be performed using the Andersen-Gill, modified Cox regression approach, for 1007 versus Placebo Anderson-Gill model.

Sample SAS® code is shown below:

```
PROC PHREG DATA=ag COVM covs(aggregate)ALPHA = 0.2;

class trt01an (REF = '1') MACROUSE SPUTUCUT/ORDER = INTERNAL PARAM =GLM;
MODEL (Tstart, Tstop) * STATUS(0) = trt01an/ RISKLIMITS TYPE3 RIDGING =
ABSOLUTE;
strata MACROUSE SPUTUCUT;
id usubjid;

RUN;
```