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

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CLINICAL STUDY PROTOCOL

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

Study Number: INS1007-201

Study Phase: 2

IND Number: 133790
EUDRACT Number: 2017-002533-32

Insmed Incorporated
10 Finderne Avenue, Building 10
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	Version Number	Amendment	Date
Original Protocol	1.0		21 June 2017
Amended Protocol	2.0	1.0	24 August 2017
Amended Protocol	3.0	2.0	12 March 2018
Amended Protocol	4.0	3.0	27 April 2018
Amended Protocol	5.0	4.0	24 September 2018

INVESTIGATOR AGREEMENT

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

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

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

I agree to conduct this study per this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements. I will use only the informed consent approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC responsible for this study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Insmed. It is, however, permissible to provide information to a subject to obtain consent.

I agree to make available to Insmed personnel, their representatives and relevant regulatory authorities, my subjects' study records to verify the data that has been entered to the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by Insmed.

I understand that Insmed may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Insmed.

IMPORTANT CONTACTS

Insmed Incorporated
10 Finderne Avenue, Building 10
Bridgewater, NJ 08807-3365

Insmed Global Clinical and Regulatory Affairs			
Name:	**Title**	**Telephone**	**e-Mail Address**
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Clinical Research Organization

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SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 5.0, DATED 24 SEPTEMBER 2018

Section Number and Title	Old Text	New Text	Rationale for Change
Important Contacts	[redacted]		Updated contact information for Regulatory Affairs personnel
Synopsis: Drug Product, Strength, Dosage Form, and Route of Administration	The study drugs (INS1007 and placebo) will be supplied by the Sponsor~~ in bottles containing 35 tablets per bottle as described below~~.		Revised to be align with details in Section 5.1
Synopsis: Efficacy Analysis	The efficacy analysis of the time to the first exacerbation will be performed for the intent-to-treat (ITT) population using Kaplan Meier curves~~, which will be generated for the treatment arms at the 2-sided significance level of 0.05~~.		Revised to align with Section 9.5.1.2
Synopsis: Data Monitoring Committee	~~The DMC members will review the data at predetermined intervals in a masked manner, with the potential for unblinded review if deemed necessary by its members.~~	The DMC members will review the data in a semi-blinded or un-blinded manner at predetermined intervals.	Revised to align with Section 3.5
3.1. Overall Study Design and Plan Screening Period (Visit 1)		Subjects whose past chest radiographic image records are not available will undergo a chest computed tomography (CT) scan during Screening (Visit 1).	Added to align with the procedures/assessments listed in Table 6 Schedule of Events
3.1. Overall Study Design and Plan Treatment Period (Visits 2 through 9)	**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,	**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,	Clarified text to ensure subject eligibility prior to randomization

Section Number and Title	Old Text	New Text	Rationale for Change
	and pregnancy test (females of child bearing potential [WOCBP] only) will be conducted. 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.	and pregnancy test (females of child bearing potential [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.	
3.1. Overall Study Design and Plan Figure 1 Study Design Diagram	Day 1 to Day ~~168~~ (24 Week Treatment Period) ~~Day 169 to Day 192 (4 weeks)~~	Day 1 to Day 169 (24 Week Treatment Period) Day 197 (±3 Days)	Updated study days in Figure 1 to align with the Schedule of Events
4.1.1. Inclusion Criteria number 5	Are current sputum producers with a history of chronic expectoration, and able to provide sputum sample during Screening;	Are current sputum producers with a history of chronic expectoration, and able to provide sputum sample during Screening. If a subject is unable to produce sputum spontaneously during Screening (Visit 1), the subject will be considered a screen failure. The subject may not undergo a sputum induction procedure during Screening (Visit 1) to meet inclusion criterion.	Added clarification to ensure that subjects do not undergo a sputum induction during Screening Additional revision to footnote "e" to align with Appendix 1
Table 6: Schedule of Events Footnote "e"	e Subjects will be required to provide a sputum sample during the specified visits. 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	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 (Section 4.1, inclusion criterion 5). On Day 1, the sputum sample should be	

Section Number and Title	Old Text	New Text	Rationale for Change
	physiotherapy should be performed first to facilitate expectoration. If chest physiotherapy fails, the sputum induction procedure detailed in the protocol ~~will~~ be performed to obtain a sputum sample.	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.	
7.3.5. Inflammatory Biomarker Levels-Sputum	If a subject is unable to produce sputum spontaneously during any visit, the subject should undergo a sputum induction procedure. The detailed sputum induction procedure is described in Appendix 1.	If a subject is unable to produce sputum spontaneously during any visit, the subject should undergo a sputum induction procedure (a subject may not undergo a sputum induction procedure during Screening [Visit 1] to meet eligibility [Section 4.1, inclusion criterion 5]). The detailed sputum induction procedure is described in Appendix 1.	
Appendix 1. Sputum Induction Guidelines		Note: If a subject is unable to produce sputum spontaneously during Screening (Visit 1), the subject will be considered a screen failure. The subject may not undergo a sputum induction procedure during Screening (Visit 1) to meet eligibility (Section 4.1, inclusion criterion 5).	
4.1.2. Exclusion Criteria number 5	Have any acute infections (including respiratory infections) that required antibiotic treatment within 4 weeks before Screening or within 12 weeks	Have any acute infections (including respiratory infections) that required antibiotic treatment within 4 weeks before Screening or within 12 weeks	Further clarified that any subject who suffers an exacerbation or infection requiring antibiotic treatment prior to randomization will be considered a screen failure

Section Number and Title	Old Text	New Text	Rationale for Change
	before Screening if the antibiotic prescription is a macrolide;	before Screening if the antibiotic prescription is a macrolide; If a subject suffers an exacerbation or infection requiring antibiotic treatment after the Screening visit, but prior to randomization, the subject will be considered a screen failure	
4.1.2. Exclusion Criteria number 23	**Medical conditions associated with the onset of non-hereditary palmoplantar keratosis:** ~~Have~~ hypothyroidism, ~~or~~ myxedema, ~~or~~ chronic lymphedema, ~~or~~ acrocyanosis, or livedo reticularis;	**Have the following medical conditions associated with the onset of non-hereditary palmoplantar keratosis:** Hypothyroidism, myxedema, chronic lymphedema, acrocyanosis, or livedo reticularis; Note: If a subject has hypothyroidism but is currently being treated, and thyroid-stimulating hormone (TSH) and/or triiodothyronine (T3)/ thyroxine (T4) are within normal ranges, the subject is allowed into the trial.	Clarified criterion to permit enrollment of eligible subjects who have hypothyroidism
7.7.6. Dermatological Assessment	The entry criteria in the study have been defined to exclude subjects with underlying dermatologic conditions that could impair the ability to detect a potential safety signal or might put the subject at increased risk. Specifically, the relevant exclusion criteria are: Have hypothyroidism, or myxedema, or chronic lymphedema, or acrocyanosis, or livedo reticularis;	The entry criteria in the study have been defined to exclude subjects with underlying dermatologic conditions that could impair the ability to detect a potential safety signal or might put the subject at increased risk. Specifically, the relevant exclusion criteria are: Have hypothyroidism, or myxedema, or chronic lymphedema, or acrocyanosis, or livedo reticularis. If a subject has hypothyroidism but is currently being treated, and TSH and/or T3/ T4 are within normal ranges, the subject is allowed into the trial.	

Section Number and Title	Old Text	New Text	Rationale for Change
4.2.2. Subject Re-Screening Procedures	Subjects who do not meet eligibility criteria during Screening may be re-screened up to 2 times if approved by Insmed's Medical Monitor.	Subjects who do not meet eligibility criteria during Screening may be re-screened up to 2 times if approved by Insmed's Medical Monitor. During Screening (Visit 1), if a subject does not qualify due to ECGs that do not meet the quality criteria, the subject can repeat the test up to 2 times without being re-screened. Subjects who need to repeat PFTs because they do not meet exclusion criterion 6 (Section 4.1.2), can repeat the test up to 2 times without being re-screened. Subjects who are considered a screen failure for reasons not related to the dental exclusion criteria (Section 4.1.2, 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.	Added clarification to permit enrollment of eligible subjects who need to repeat an ECG and/or PFT that are not clinically significant Under re-screening procedures, clarified dental exam requirement for subjects who screen fail for reasons not related to the dental exclusion criteria
4.1.2. Exclusion Criteria number 6	6. Are unable to perform technically acceptable spirometry meeting American Thoracic Society (ATS)/European Thoracic Society (ERS) acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 during Screening~~.~~	6. Are unable to perform technically acceptable spirometry meeting American Thoracic Society (ATS)/European Thoracic Society (ERS) acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV1 during Screening a. Subjects who need to repeat PFTs because they do not meet the exclusion criterion can repeat the	

Section Number and Title	Old Text	New Text	Rationale for Change
4.1.2. Exclusion Criteria number 19	test up to 2 times without being re-screened. 19. Have a baseline-corrected QT interval by Fridericia (QTcF) > 450 milliseconds (males) or 470 milliseconds (females) or history of congenital long QT syndrome, or Torsades de Pointes or other abnormal ECG at Screening or Baseline (unless the ECG findings are not clinically significant and are approved by the Investigator and documented by signature)~~;~~	test up to 2 times without being re-screened. 19. Have a baseline-corrected QT interval by Fridericia (QTcF) > 450 milliseconds (males) or 470 milliseconds (females) or history of congenital long QT syndrome, or Torsades de Pointes or other abnormal ECG at Screening or Baseline (unless the ECG findings are not clinically significant and are approved by the Investigator and documented by signature) a. If a subject does not qualify due to ECGs that do not meet the quality criteria, the subject can repeat the test up to 2 times without being re-screened.	
5.1.9. Drug Usage and Accountability	The study drugs are to be prescribed only by the Investigators or sub-Investigators ~~named on the Form FDA 1572~~.	The study drugs are to be prescribed only by the Investigators or sub-Investigators participating in the trial.	Updated to cover all global study sites
5.3. Prohibited Medications	Use of any immunomodulatory agents (eg, bortezomib, ixazomib, and thalidomide) is prohibited during the study ~~until~~ Visit 10 (EOS). Continuous use of high dose non-steroidal anti-inflammatory drugs is prohibited during the study ~~until~~ Visit 10 (EOS) unless the use is considered necessary per Investigator discretion. Medications that may cause a palmoplantar keratoderma are prohibited during the study ~~until~~ Visit 10 (EOS).	Use of any immunomodulatory agents (eg, bortezomib, ixazomib, and thalidomide) is prohibited during the study through Visit 10 (EOS). Continuous use of high dose non-steroidal anti-inflammatory drugs is prohibited during the study through Visit 10 (EOS) unless the use is considered necessary per Investigator discretion. Medications that may cause a palmoplantar keratoderma are prohibited during the study through Visit 10 (EOS).	Clarified that the duration is through Visit 10

Section Number and Title	Old Text	New Text	Rationale for Change
5.3. Prohibited Medications Table 1: Prohibited Medications (May Cause Palmoplantar Keratoderma) Table 2: List of Moderate and Strong CYP2D6 and CYP2C8 Inhibitors (not to be Co-Administered With CYP3A4/5 Inhibitors but Otherwise Permitted)	~~6~~ Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up Moderate CYP2D6 Inhibitors ~~6~~ weeks prior to Day1 to 28-day Safety Follow-Up	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up Moderate CYP2D6 Inhibitors 4 weeks prior to Day1 to 28-day Safety Follow-Up	Corrected typos in Tables 1 and 2
5.4. Permitted Medications and Procedures	However, except under unforeseeable clinical circumstances, the airway clearance maintenance treatment/procedures and pulmonary rehabilitation should continue unchanged throughout the duration of the study ~~until~~ Visit 10 (EOS).	However, except under unforeseeable clinical circumstances, the airway clearance maintenance treatment/procedures and pulmonary rehabilitation should continue unchanged throughout the duration of the study through Visit 10 (EOS).	Clarified that the duration is through Visit 10
Table 6: Schedule of Events Prior/Concomitant Medications		X	Indicated that review and documentation of prior and concomitant medications must also take place during Screening (Visit 1) to align with Section 6.1.1.
Table 6: Schedule of Events Collection of PK sample for INS1007 at End of Study Visit	X Intense PK ~~Trough~~ Sampling	X Intense PK Sampling	Revised the table to be consistent with corresponding footnote "j"

Section Number and Title	Old Text	New Text	Rationale for Change
Table 6: Schedule of Events Footnote "c" Vital Signs (BP, HR, T, RR) Clinical Laboratory Tests (Hematology, Blood Chemistry and Urinalysis)	c Clinical laboratory blood samples should be collected prior to the first dose of the study drug on Day 1.	c Vital signs and clinical laboratory blood samples should be collected prior to the first dose of the study drug on Day 1.	Revised footnote to align with Section 9.5.1.3.3 Added footnote to corresponding rows in the Schedule of Events table
Table 6: Schedule of Events Footnote "g" **7.7.5. Dental Examination**	g ~~Subjects who are edentulous will not be required to have the dental examination.~~ All other subjects who meet all inclusion but none of the 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.	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 but none of the 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 (Section 4.1.2, 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.	Revised because edentulous patients may have denture sores produced by dentures. An examination and re-instruction denture maintenance may prevent any further deterioration during the study period. Clarified dental exam requirement for subjects who screen fail for reasons not related to the dental exclusion criteria
Table 6: Schedule of Events	i Subjects will complete the QOL-B and LCQ every 2 weeks until Visit 10.	i Subjects will complete the SGRQ, QOL-B, and LCQ every 2 weeks until	Revised footnote to align with Section 3.1

Section Number and Title	Old Text	New Text	Rationale for Change
Footnote "i" SGRQ Completion and Review	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.	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.	Added footnote to corresponding row in the Schedule of Events table
7.2.1. Quality of Life Questionnaire-Bronchiectasis	The QOL-B will be provided to the study subjects in an electronic format on a hand-held computer tablet after randomization. Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).	The QOL-B will be provided to the study subjects in an electronic format on a hand-held computer tablet after randomization. Subjects will be required to complete the QOL-B after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).	Revised to align with Section 3.1
7.3.1. Leicester Cough Questionnaire	The LCQ will be provided to the study subjects in an electronic format on a handheld computer tablet after Randomization. Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).	The LCQ will be provided to the study subjects in an electronic format on a handheld computer tablet after Randomization. Subjects will be required to complete the LCQ after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).	Revised to align with Section 3.1

Section Number and Title	Old Text	New Text	Rationale for Change
7.3.2. St. George's Respiratory Questionnaire	The SGRQ will be provided to the study subjects in an electronic format on a handheld computer tablet after randomization. Subjects will complete the questionnaire directly on the computer tablet at Baseline (Visit 2), Week 12 (Visit 6) and Week 24 (Visit 9). It is important for the site staff to remind the subjects to bring their computer tablets with them to each clinic visit.	The SGRQ will be provided to the study subjects in an electronic format on a handheld computer tablet after randomization. Subjects will be required to complete the SGRQ after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet at Baseline (Visit 2), Week 12 (Visit 6) and Week 24 (Visit 9). It is important for the site staff to remind the subjects to bring their computer tablets with them to each clinic visit.	Revised to align with Section 3.1
Table 6: Schedule of Events Footnote "j" **7.6.1. Pharmacokinetic Sampling** **Appendix 4. Intense Pharmacokinetic Sampling Scheme**		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). At Visits 2 and 4, subjects will be fed after the 1-hour blood draw.	Added instructions on feeding time for subjects who undergo intensive PK sampling at 1, 2, 3, 4, 6, and 8 hours post-dose
Table 6: Schedule of Events **6.1.1. Visit 1 (Days -42 to -1)**		Child–Pugh Score (only for subjects whose liver function tests are abnormal and suspected to have chronic liver disease to assess for eligibility)	Added Child-Pugh Score to Table 6 and Section 6.1.1 to align with Section 7.4.8

Section Number and Title	Old Text	New Text	Rationale for Change
7.5.5. Concomitant Medications and Procedures	Review and documentation of prior and concomitant medications for each subject will be collected from Visit 2 (Baseline, Day 1) ~~until~~ Visit 10 (EOS, Day 197), and recorded in the study source document and eCRF. Concomitant procedures will be collected from Visit 1 (Baseline, Day 1) ~~until~~ Visit 10 (EOS, Day 197).	Review and documentation of prior and concomitant medications for each subject will be collected from Visit 2 (Baseline, Day 1) through Visit 10 (EOS, Day 197), and recorded in the study source document and eCRF. Concomitant procedures will be collected from Visit 1 (Baseline, Day 1) through Visit 10 (EOS, Day 197).	Clarified that the duration is through Visit 10
7.7.5. Dental Examination	All other subjects who meet all inclusion but none of the exclusion criteria except the dental exclusion criteria are required to have a dental examination that includes a full-~~month~~ dental radiography and oral examination to evaluate the conditions of oral soft tissue, gingiva and teeth by the study designated local dentist (preferably a periodontist) during Visit 1 (Screening). Subjects who have the images of a full-~~month~~ dental radiography that are performed within 6 months of Visit 1 (Screening) and available for review at Visit 1 are not required to have another dental radiography done during Visit 1.	All other subjects who meet all inclusion but none of the exclusion criteria except the dental 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 by the study designated local dentist (preferably a periodontist) during Visit 1 (Screening). Subjects who have the images of a full- mouth dental radiography that are performed within 6 months of Visit 1 (Screening) and available for review at Visit 1 are not required to have another dental radiography done during Visit 1.	Corrected typo
8.4.1. Period of Observation for Adverse Events		All AEs will be followed until the resolution or stabilization of the AEs.	Added to clarify that subjects should remain under observation until the resolution or consolidation of the adverse effects. Database lock will occur at the designated times, but follow-up of adverse events will continue until resolution or stabilization.

Section Number and Title	Old Text	New Text	Rationale for Change
8.4.2. Serious Adverse Events	Deaths and life-threatening events with any possible relationship to a study intervention must be reported to the ~~FDA~~ by telephone or fax as soon as possible, but within 7 calendar days of notification to Insmed. This initial report must be followed by a more complete written report within ~~8 additional~~ calendar days. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the ~~FDA~~ in the Investigational New Drug annual report and ~~to the European Medicines Agency~~ in the Drug Safety Update Report.	Deaths and life-threatening events with any possible relationship to a study intervention must be reported to the Regulatory Agencies by telephone or fax as soon as possible, but within 7 calendar days of notification to Insmed. This initial report must be followed by a more complete written report within 15 calendar days. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the Regulatory Agencies in the Investigational New Drug annual report and the Drug Safety Update Report, as appropriate.	Updated to adhere to current regulatory reporting requirement
9.5.2.1. Pharmacokinetic Analysis	For subjects not participating in the PK sub-study, INS1007 plasma concentration data from this study will be pooled with data from other studies for the purposes of developing a population PK model.	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. INS1007 plasma concentration data from this study will be pooled with data from other studies for the purposes of developing a population PK (PPK) model.	Added to align with the protocol synopsis
9.5.2.2. Pharmacodynamic Analysis		The NE activity in sputum and blood will be calculated as percent inhibition from the pre-treatment activity and normalized by ANC (blood only). Pre-treatment value is defined as the mean value of NE activities at Screening and Baseline and will be listed and summarized together with the ANC measurements.	Added to align with the protocol synopsis

Section Number and Title	Old Text	New Text	Rationale for Change
13. References		Kuna P, Jenkins M, O'Brien CD, Fahy WA. AZD9668, a neutrophil elastase inhibitor, plus ongoing budesonide/formoterol in patients with COPD. Respir Med. 2012 Apr;106(4):531-539.	Added literature reference for citation in Section 1.5.1
Throughout	Corrected grammatical, mechanical, and typographical errors for clarity and consistency Updated the List of Abbreviations and Definitions of Terms and the use of abbreviations throughout the document		

SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 4.0, DATED 27 APRIL 2018

Section Number and Title	Old Text	New Text	Rationale for Change
8.4.1 Period of Observation for Adverse Events	For the purposes of this study, the period of observation for collection of ~~all~~ AEs will be from the time the subject signs the ICF until ~~the resolution or stabilization of the adverse events.~~ All AEs ~~will~~ be recorded on the AEs Form of the eCRF. In the safety analysis, 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 summarized as medical history and not as a TEAE unless the event meets the definition of an SAE as defined below.	For purposes of this study, the period of observation for collection of any AEs will be from the time the subject signs the ICF until 30 days after the final dose of study drug or to the date of subject's End of Study Visit, whichever date is later. All AEs should be recorded on the AEs Form of the eCRF and should be observed until the resolution or stabilization of the adverse events. In the safety analysis, 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 summarized as medical history and not as a TEAE unless the event meets the definition of an SAE as defined below.	Section revised to clarify the duration of adverse event data collection following last administration of study drug and ensure consistency with schedule of events by taking into consideration time allocated for visit windows.
3.3.4.1 Study Discontinuation	If the study is prematurely terminated, all subjects who received a dose of any of the study drugs and have not completed their study period will be discontinued from the study immediately; all the safety procedures (refer to safety procedures during Visit 9) required to be performed will be conducted. All discontinued subjects will be followed up by a phone call 28 days after discontinuation for collection of AEs.	If the study is prematurely terminated, all subjects who received a dose of any of the study drugs and have not completed their study period will be discontinued from the study immediately; all the safety procedures (refer to safety procedures during Visit 9) required to be performed will be conducted. All discontinued subjects will be followed up by a phone call 28 days (+/- 3 days) after discontinuation for collection of AEs.	Section revised to enable a window of +/- 3 days for data collection consistent with time windows allowed for study visits.
5.3 Prohibited Medications	**Table 1** Required Washout Period	**Table 1** Required Washout Period	Section revised to enable a window of +/- 3 days consistent with time windows allowed for study visits.

Section Number and Title	Old Text	New Text	Rationale for Change
	6 weeks prior to Day1 to 28-day Safety Follow-up	6 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-up	
	Table 2 Required Washout Period Moderate CYP2D6 Inhibitors 6 weeks prior to Day1 to 28-day Safety Follow-Up Strong CYP2D6 Inhibitors 4 weeks prior to Day1 to 28-day Safety Follow-Up Moderate CYP2C8 Inhibitors 4 weeks prior to Day1 to 28-day Safety Follow-Up Strong CYP2C8 Inhibitors 4 weeks prior to Day1 to 28-day Safety Follow-Up	**Table 2** Required Washout Period Moderate CYP2D6 Inhibitors 6 weeks prior to Day1 to 28-day (+/- 3days) Safety Follow-Up Strong CYP2D6 Inhibitors 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up Moderate CYP2C8 Inhibitors 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up Strong CYP2C8 Inhibitors 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up	Section revised to enable a window of +/- 3 days consistent with time windows allowed for study visits.
	Table 3 Required Washout Period Moderate CYP3A4/5 Inhibitor 4 weeks prior to Day1 to 28-day Safety Follow-Up Strong CYP3A4/5 Inhibitors	**Table 2** Required Washout Period Moderate CYP3A4/5 Inhibitor 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up Strong CYP3A4/5 Inhibitors	Section revised to enable a window of +/- 3 days consistent with time windows allowed for study visits.

Section Number and Title	Old Text	New Text	Rationale for Change
	4 weeks prior to Day1 to 28-day Safety Follow-Up	4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up	
	Table 4 Required Washout Period Moderate CYP3A4/5 Inhibitors 4 weeks prior to Day1 to 28-day Safety Follow-Up Strong CYP3A4/5 Inducers 4 weeks prior to Day1 to 28-day Safety Follow-Up	**Table 4** Required Washout Period Moderate CYP3A4/5 Inhibitors 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up Strong CYP3A4/5 Inducers 4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up	Section revised to enable a window of +/- 3 days consistent with time windows allowed for study visits.

SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 3.0, DATED 12 MARCH 2018

Section Number and Title	Old Text	New Text	Rationale for Change
1.3.2 Clinical Experience	INS1007 has been assessed in 2 healthy volunteer studies (D6190C0001 and D6190C00003).	INS1007 has been assessed in 2 healthy volunteer studies (D6190C0001 and D6190C00003). Study D6190C00001 Study D6190C00001 was a Phase 1, randomized, single-blind, placebo-controlled, multi-part study in healthy adult male volunteers. Part 1a was a single ascending dose (SAD) study in which 45 subjects received either placebo (15 subjects) or INS1007 (5, 15, 35, 50, or 65 mg [6 subjects per dose level]) under fasting conditions. Part 1b was a single-dose food effect study in which 8 subjects (Cohort 3 from Part 1a after a washout of at least 7 days) received either placebo (3 subjects) or 35 mg INS1007 (5 subjects) after a high-fat breakfast. Part 2 was a multiple ascending dose (MAD) study in which 36 subjects (who did not participate in Part 1) received either placebo (12 subjects) or INS1007 (6 subjects received 10 mg/day for 21 days, 8 subjects received 25 mg/day for 28 days, and 10 subjects received 40 mg/day for 28 days) under fasting conditions. The safety variables for INS1007 were adverse events (AEs); safety laboratory assessments (hematology, clinical chemistry, urinalysis); vital signs (pulse rate, blood pressure, oral body	Section revised to provide additional information on the completed Phase 1 studies.

Section Number and Title	Old Text	New Text	Rationale for Change
		temperature); 12-lead paper and digital electrocardiogram (ECG, pre-hospital ECG [pECG], and direct ECG [dECG]); telemetry; physical examination results (including evaluation of gingiva and teeth, and evaluation of palms and soles). In addition, part 2 laboratory assessments also included neutrophil phagocytosis, oxidative burst, spermatogram [fertile male subjects participating in Cohort 3 and onwards] and reproductive hormones [Cohort 3 and onwards]); Study D6190C00003 Study D6190C00003 was an open-label, fixed sequence, 3-period, drug-drug interaction (DDI) study of the effects of concomitant verapamil (moderate CYP3A4 inhibitor) and itraconazole (strong CYP3A4 inhibitor) on the single-dose PK of INS1007 and its tolerability and safety in healthy adult male volunteers. The study consisted of 3 periods with at least a 7-day washout between Periods 1 and 2 and at least a 14-day washout between Periods 2 and 3. During Period 1, 15 subjects received a single dose of INS1007 (25 mg). During Period 2, the same subjects received verapamil (240 mg, extended release formulation) on Days 1 through 10 plus a single dose of INS1007 (25 mg) on Day 5. During Period 3, the same subjects received itraconazole (200 mg as oral solution of 10 mg/mL) twice on Day 1 and then once daily on Days 2 through 11 plus a single dose of INS1007 (25 mg) on Day 6. All drugs were administered under fasting conditions.	

Section Number and Title	Old Text	New Text	Rationale for Change
		Safety variables included AEs, vital signs (systolic and diastolic blood pressure, pulse rate and temperature), electrocardiograms (safety and dECGs), laboratory assessments (hematology, clinical chemistry and urinalysis) and physical examinations (including evaluation of gingiva and teeth and evaluation of palms and soles). Viral serology, tuberculosis (TB) screen and urine drugs of abuse, alcohol and cotinine were assessed for eligibility. The use of concomitant medications was also assessed and reported.	
1.5.2.2 Infections **8.3.3** Other Infections	All serious infections and all specific infections believed to be associated with neutropenia, such as ~~skin infection~~, soft tissue infection, urinary tract infection~~, gingivitis~~ should be entered in the infection module of the electronic case report form (eCRF).	All serious infections and all specific infections believed to be associated with neutropenia, such as soft tissue infection, urinary tract infection should be entered in the infection module of the eCRF.	All skin and gingivitis events should be reported in the specific page of AEs of special interest for skin and dental adverse events.
Synopsis and Section 2.1.2 Secondary Objectives	1.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. 2. 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. 3. To evaluate the effect of INS1007 compared with placebo on the concentration of active neutrophil elastase	1.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. 2. 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. 3. To evaluate the effect of INS1007 compared with placebo on the concentration of active neutrophil elastase	Details on calculation of NE activity will be described in the Statistical Analysis Plan.

Section Number and Title	Old Text	New Text	Rationale for Change
	(NE) in sputum, as measured by the difference between the pre-treatment concentration ~~(defined as the average of the values at Screening and Day 1)~~ and on-treatment concentration ~~(defined as the average of the values at weeks 12 and 24)~~. 4. To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period.	(NE) in sputum, as measured by the difference between the pre-treatment concentration and on-treatment concentration. 4. To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period	
Synopsis and Section 2.1.3 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, and 28. To evaluate the effect of INS1007 compared with placebo on the concentration of active NE in reagent-	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, and 28. To evaluate the effect of INS1007 compared with placebo on the concentration of active NE in reagent-	Edits implemented to align Exploratory Study Objectives with the corresponding Exploratory Study Endpoints.

Section Number and Title	Old Text	New Text	Rationale for Change
	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 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 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 ~~and urine~~ at Weeks 2, 4, 12, 24, and 28. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters (as measured by spirometry) over the 24-week treatment period: Forced vital capacity (FVC) Peak expiratory flow rate (PEFR) Forced expiratory flow (FEF) 25 to 75% (FEF_{25-75}) To evaluate the effect of INS1007 compared with placebo on the total	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) 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 parameters as	

Section Number and Title	Old Text	New Text	Rationale for Change
	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 FEF), stratified by Baseline Bronchiectasis Severity Index, 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 FEF_{25-75}), stratified by the presence or absence of *Pseudomonas aeruginosa* at Screening, over the 24-week treatment period. To evaluate the effect of INS1007 compared with placebo on the use of rescue medications over the 24-week treatment period. To evaluate the effect of INS1007 compared with placebo on hospitalizations for pulmonary exacerbations 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.	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 parameters 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 parameters as measured by spirometry (Forced expiratory flow [FEF] 25 to 75% [FEF_{25-75}]) 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 FEF_{25-75}), stratified by Bronchiectasis Severity Index score at baseline, 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	

Section Number and Title	Old Text	New Text	Rationale for Change
		FEF_{25-75}), 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 pulmonary exacerbations 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.	
Synopsis and Section 3.2.3 Exploratory Endpoints	Change from Baseline in QOL-B scores (all domains excluding the Respiratory Symptoms Domain) over the 24 -week treatment period. Change from Baseline in LCQ score over the 24-week treatment period. Change from Baseline in SGRQ total score over the 24-week treatment period. Change in concentration of active NE in sputum from pre-treatment to Weeks 2, 4, and 28.	Change from Baseline in QOL-B scores (all domains excluding the Respiratory Symptoms Domain) over the 24 -week treatment period. Change from Baseline in QOL as assessed by the LCQ score over the 24-week treatment period. Change from Baseline in SGRQ total score over the 24-week treatment period. Change in concentration of active NE in sputum from pre-treatment to Weeks 2, 4, and 28.	Edits implemented to align Study Objectives with the corresponding Study Endpoints.

Section Number and Title	Old Text	New Text	Rationale for Change
	Change in concentration of active NE in reagent-stimulated blood from pre-treatment to Weeks 2, 4, 12, 24, and 28. Change from Baseline in sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28. Change from Baseline in inflammatory and tissue degradation biomarker levels in sputum at Weeks 2, 4, 12, 24, and 28 (the biomarkers that may be explored consist of proteinase 3 and cathepsin G). Change from Baseline in inflammatory and tissue degradation biomarker levels in blood at Weeks 2, 4, 12, 24, and 28 (the biomarkers that may be explored consist of absolute neutrophil count (ANC), proteinase 3, and cathepsin G). Change from Baseline in desmosine in urine at Weeks 2, 4, 12, 24, and 28. Change from Screening ~~of~~ FVC at Weeks 12 and 24. Change from Screening ~~of~~ PEFR at Weeks 12 and 24. Change from Screening ~~of~~ FEF_{25-75} at Weeks 12 and 24. Total duration (in days) of exacerbations, per subject, over the 24-week treatment period. Frequency of use of rescue medications over the 24-week treatment period (rescue medications include short-acting beta agonists, short-acting muscarinic agonists, newly prescribed long-acting beta agonists, long-acting anti-muscarinic agonists, and oxygen).	Change in concentration of active NE in reagent-stimulated blood from pre-treatment to Weeks 2, 4, 12, 24, and 28. Change from Baseline in sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28. Change in concentration of active NE in sputum (stratified by sputum color) at baseline from pre-treatment to Weeks 2, 4, 12, and 28. Change from Baseline in inflammatory and tissue degradation biomarker levels in sputum (the biomarkers which may be assessed are e.g. proteinase 3 and cathepsin G) at Weeks 2, 4, 12, 24, and 28. Change from Baseline in inflammatory and tissue degradation biomarker levels in blood (biomarkers which may be assessed are e.g.ANC, proteinase 3, and cathepsin G) at Weeks 2, 4, 12, 24, and 28. Change from Baseline in tissue degradation marker level in urine (desmosine) at Weeks 2, 4, 12, 24, and 28. Change from Screening in FVC at Weeks 12 and 24. Change from Screening in PEFR at Weeks 12 and 24. Change from Screening in FEF_{25-75} at Weeks 12 and 24. Total duration (in days) of exacerbations, per subject, over the 24-week treatment period. Total number of exacerbations per subject over the 24-week treatment period.	

Section Number and Title	Old Text	New Text	Rationale for Change
	Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period.	Time to first pulmonary exacerbation, exacerbation rate, QOL Measures, and pulmonary function parameters (FEV1, FVC, PEFR, and $FEF_{25-75)}$, stratified Bronchiectasis Severity Index (BSI) score at baseline, over the 24-week treatment period. 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 *Pseudomonas aeruginosa* at Screening, over the 24-week treatment period. 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. Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period. Descriptive assessment of the change in inflammatory and tissue degradation biomarkers and concentration of active NE in blood, sputum, and urine, over the 24-week treatment period.	
Synopsis Study Design and 3.1 Overall Study Design and Plan	**Screening Period** There will be a screening period of up to 4-weeks per subject. During the screening period, the subject's demographic information, medical history and smoking history will be obtained, a physical exam,	**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,	Dental cleaning procedures may require 2 sessions at the dental office. Scheduling such appointments can make it difficult to randomize a patient within 4 weeks. The extension of the

Section Number and Title	Old Text	New Text	Rationale for Change
	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, ECG, and pulmonary function test (PFT). ~~and periodontal cleaning and examination~~ will be conducted.	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, and pulmonary function test (PFT) will be conducted. Periodontal examination and dental cleaning procedures for inclusion should be performed prior to randomization.	screening period from 4 to 6 weeks will allow for the finalization of all procedures prior to randomization.
3.1 Overall Study Design and Plan	**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 (females of child bearing potential [WOCBP] only) will be conducted. After re-confirming their eligibility, subjects will be randomized ~~via an interactive response technology (IRT)~~ 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.	**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 (females of child bearing potential [WOCBP] only) will be conducted. 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.	To specify the system used to randomize patients
Synopsis Study Design and 3.1 Overall Study Design and Plan	**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.	**End-of-Study Visit (Visit 10)** Subjects will be required to have an EOS visit (Visit 10) at week 28 to collect blood, sputum and urine samples for biomarker assessment and pregnancy test for WOCBP 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.	

Section Number and Title	Old Text	New Text	Rationale for Change
Synopsis: Treatment Duration 3.1 Overall Study Design and Plan 3.3.2 Study Duration	Each subject will receive study treatment for 24 weeks. The entire study is scheduled to take a maximum of ~~32~~ weeks for each individual subject from Screening (Visit 1) to the End of Study (Visit 10).	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 (Visit 10).	Study duration increased by 2 weeks due to allowance for a screening period up to 6 weeks.
4.1.1 Inclusion Criteria	Inclusion criteria #8 Women must be post-menopausal, surgically sterile, or using highly effective contraception methods (i.e., methods that alone or in combination achieve <1% unintended pregnancy rates per year). Such methods include true abstinence (refraining from heterosexual intercourse during the study), combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone-releasing systems, or vasectomized partner. All women of childbearing potential (WOCBP) must have a negative pregnancy test before randomization.	Inclusion criteria #8 Women must be post-menopausal, (defined as no menses for 12 months without an alternative medical cause), surgically sterile, or using highly effective contraception methods (i.e., methods that alone or in combination achieve <1% unintended pregnancy rates per year) from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study), combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom), intrauterine devices, intrauterine hormone-releasing systems, or vasectomized partner. All women of childbearing potential (WOCBP) must have a negative pregnancy test before randomization. **Note:** Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual life style of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus),	Section was revised: To add definition of "women of childbearing potential" To advise female participants to use contraception for a minimum of 90 after the last dose: Per Clinical Trial Facilitation Group (CTFG) recommendations, contraception should be maintained during treatment and until the end of relevant systemic exposure. The proposed duration of 90 days surpasses the end of relevant systemic exposure and is recommended to be consistency with the recommendation made to male participants. To clarify that hormonal contraception methods should be supplemented with a double barrier, considering it cannot be ruled out, based *in vitro* data, that INS1007 is a CYP3A4 inducer *in vivo*. Per CTFG recommendations: "If an interaction with contraceptive steroids has been observed or is suspected, but the effect is

Section Number and Title	Old Text	New Text	Rationale for Change
		spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.	considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom)." To clarify that abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual life style of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. To remove the statement "the definition of effective contraception will be based on the judgement of the investigator".
4.1.1 Inclusion Criteria	Inclusion criteria #9 Males with female partners of childbearing potential must be using effective contraception ~~(the definition of effective contraception will be based on the judgement of the Investigator)~~ from Day 1 to at least ~~30~~ days after the last dose; **Note:** Male subjects will be advised of the potential toxicity to sperm observed in nonclinical studies and will be advised not to participate in the study if they plan to father a child in the future.	Inclusion criteria #9 Males with female partners of childbearing potential must be using effective contraception from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study), combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone-releasing systems, or vasectomized partner. **Note:** Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual life	Section was revised: To list acceptable methods of contraception: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, and sexual abstinence.

Section Number and Title	Old Text	New Text	Rationale for Change
		style of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. **Note:** Male subjects will be advised of the potential toxicity to sperm observed in nonclinical studies and will be advised not to participate in the study if they plan to father a child in the future.	To clarify that abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual life style of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. To remove the statement "the definition of effective contraception will be based on the judgement of the investigator". To advise male participants to use contraception for a minimum of 90 days after the last dose. **Justification:** Risk mitigation due the testicular toxicities observed in the 6 months dog study and in consideration of the life-cycle and duration of spermatogenesis.
4.1.2 Exclusion Criteria		Exclusion criteria #33 Have a clinical diagnosis of Papillon-Lefèvre Syndrome.	Section revised to exclude patients who have been diagnosed with Papillon-Lefèvre syndrome and have the phenotype that characterizes it, as INS1007 will offer no benefit.
4.2.1 Reasons for Withdrawal/Early Discontinuation	A subject may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator. When this occurs, the	A subject may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator. When this occurs, the subject should complete all the procedures	Section revised to clarify that patients discontinuing the treatment due to adverse effects should remain under observation until the resolution or consolidation of the

Section Number and Title	Old Text	New Text	Rationale for Change
	subject should complete all the procedures at the Visit 9 (End of Treatment) Visit.	at the Visit 9 (End of Treatment) Visit. Subjects who discontinue the treatment due to adverse events should remain under observation until the resolution or stabilization of the adverse events.	adverse effects. Database lock will occur at the designated times, but follow-up of adverse events will continue until resolution or stabilization.
4.2.2 Subject Re-Screening Procedures	Subjects who do not meet eligibility criteria during Screening may be re-screened up to 2 times if approved by Insmed's Medical Monitor. If a subject has 1 or 2 abnormal laboratory values at screening (considered non-clinically significant by the investigator) the site can re-test those abnormal values up to 2 times through the central laboratory, this will not be considered a re-screening procedure.	Subjects who do not meet eligibility criteria during Screening may be re-screened up to 2 times if approved by Insmed's Medical Monitor.	A patient who does not meet eligibility criteria should be screened failed. If deemed appropriate, the PI can re-screen the patient.
5.1.4 Unblinding Procedures	In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study treatment is not sufficient and the study treatment must be unblinded to evaluate further course of action, the Investigator ~~should~~ contact the Insmed Medical Monitor or appropriate Insmed study personnel prior to the unblinding. The Investigator must be able to confirm that unblinding of the subject is necessary and directly impacts the subject's immediate medical management or welfare of the subject. The subject will be considered discontinued from the study. If this is not possible, the Investigator must notify the Sponsor as soon as possible. The date and reason for unblinding must be documented and signed by the study Investigator. The originally signed copy is maintained in the study file at the site, and	In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study treatment is not sufficient and the study treatment must be unblinded to evaluate further course of action, the Investigator can unblind study treatment for a specific patient. It is suggested that the Investigator contact the Insmed Medical Monitor or appropriate Insmed study personnel prior to the unblinding. The Investigator must be able to confirm that unblinding of the subject is necessary and directly impacts the subject's immediate medical management or welfare of the subject. The subject will be considered discontinued from the study. If this is not possible, the Investigator must notify the Sponsor as soon as possible. The date and reason for unblinding must be documented and signed by the study	Revised to clarify that it is the Investigator's decision to unblind a patient.

Section Number and Title	Old Text	New Text	Rationale for Change
	a copy is provided to the Sponsor or its designee. The date and reason for the unblinding is also entered in the study electronic case report form (eCRF) and any associated AE reports.	Investigator. The originally signed copy is maintained in the study file at the site, and a copy is provided to the Sponsor or its designee. The investigator should follow the steps in the Medidata Balance RTMS system and enter the unblinding date and reason. The date and reason for the unblinding is also entered in the study electronic case report form (eCRF) and any associated AE reports.	
5.3 Prohibited Medications	As a rule, no companion medication that has been tolerated and is considered necessary by the Investigator for the treatment of the subjects' underlying disease or comorbidities shall be withheld in any subject to fulfill eligibility for this study. However, where possible, alternative treatments with a lower risk or potential for interacting with INS1007 should be considered.	As a rule, no companion medication that has been tolerated and is considered necessary by the Investigator for the treatment of the subjects' underlying disease or comorbidities shall be withheld in any subject to fulfill eligibility for this study.	Revised to clarify that no medication should be changed if it is considered necessary by the Investigator.
5.4 Permitted Medications and Procedures	Any concurrent ongoing medications, including over-the-counter drugs ~~and herbal supplements,~~ are allowed if not prohibited by the protocol (see Section 5.3).	Any concurrent ongoing medications, including over-the-counter drugs are allowed if not prohibited by the protocol (see Section 5.3).	Section revised to remove reference to herbal supplements: **Justification:** Section 5.3 acknowledges medicines for which prescription is required.
5.4 Permitted Medications and Procedures Table 5: Minimum Time Intervals for Restricted Medication Use Prior to Reversibility/Spirometry Testing	**Minimal Time Interval from Last Medication Dose** ~~Pre~~-Bronchodilator Testing	**Minimal Time Interval from Last Medication Dose** Prior to post-Bronchodilator Testing	The evaluation of lung function parameters is post-bronchodilation.

Section Number and Title	Old Text	New Text	Rationale for Change
6.2.2 Visit 3 (Week 2, Day 15)	Study drug dispensing and review of dosing diary	Review of dosing diary	No study drug dispensing as subjects are dosed monthly.
Table 6: Schedule of Events Study Drug Dispense, Accountability of Returned Drug, and Review of Dosing Diary	X	X[n] Added footnote: [n] No study drug dispensing at this Visit	No study drug dispensing required as subjects are dosed monthly.
6.2.9 Visit 10 (Week 28, Day 197, End of Study)		Added: Physical Examination Added: Urine pregnancy test for WOCBP	
Table 6: Schedule of Events		Visit 10: Physical Examination Added: Urine pregnancy test for WOCBP	
6.1.1 through 6.2.9 Visit 1 through Visit 10		Added: Special laboratory tests (C-reactive protein, prothrombin time)	
Table 6: Schedule of Events		Added to Visits 1 through 10: Special laboratory tests (C-reactive protein, prothrombin time)	
Table 6: Schedule of Events **Appendix 4:** Intense Pharmacokinetic Sampling Scheme	Footnote J: In addition, a trough PK sample (predose of INS1007) will be collected at Visits 3, 6, 9 ~~and 10~~.	Footnote J: In addition, a trough PK sample (predose of INS1007) will be collected at Visits 3, 6, and 9. Collection of PK sample at visit 10 will be done anytime either pre- or post-dose during the visit.	To clarify that at visit 10 a PK sample will be collected at any time, as described in Section 7.6.1. At visit 10 patients will have been off medication for 4 weeks.
7.2.2 Pulmonary Function Test	Pulmonary function test by spirometry (FEV1, FVC, PEFR, and FEF_{25-75}) will be performed per the American Thoracic Society (ATS/European Respiratory Society [ERS]) criteria (Miller et al, 2005) at Visit 1 (Screening), Visit 6, and Visit 9 (refer to Table 6).	Post-bronchodilator pulmonary function test by spirometry (FEV1, FVC, PEFR, and FEF_{25-75}) will be performed per the American Thoracic Society (ATS/European Respiratory Society [ERS]) criteria (Miller et al, 2005) at Visit 1 (Screening), Visit 6, and Visit 9 (refer to Table 6).	Section revised to clarify the procedures to perform bronchodilation and the timing of lung function tests.

Section Number and Title	Old Text	New Text	Rationale for Change
	Subjects should be advised to withhold short-acting inhaled drugs (eg, the β-agonist albuterol/salbutamol or the anticholinergic agent ipratropium bromide) within 6 hours prior to the test. Long-acting β-agonist bronchodilators (e.g. salmeterol or formoterol) or long-acting muscarinic bronchodilators (eg, tiotropium) or oral therapy with aminophylline or slow release β-agonists should be withheld for 12-24 hours depending on the medication used (refer to Table ~~6~~) for the minimum time intervals for a list of restricted medications) prior to testing.	Subjects should be advised to withhold short-acting inhaled drugs (eg, the β-agonist albuterol/salbutamol or the anticholinergic agent ipratropium bromide) within 6 hours prior to the test. Long-acting β-agonist bronchodilators (e.g. salmeterol or formoterol) or long-acting muscarinic bronchodilators (eg, tiotropium) or oral therapy with aminophylline or slow release β-agonists should be withheld for 12-24 hours depending on the medication used (refer to Table 5) for the minimum time intervals for a list of restricted medications) prior to testing. Post-bronchodilator spirometry tests will be performed per the following instructions: When an inhaled Short Acting Beta 2 agonist (SABA) is used, 4 puffs of Albuterol, levalbuterol, or Terbutaline will be administered. A post-bronchodilator PFT will be performed 15 to 30 minutes after the administration of Albuterol or levalbuterol. If another SABA is used, Insmed should be contacted for further directions. When an inhaled Short Acting Muscarinic Antagonist (SAMA) is used, 4 puffs of Ipratropium will be administered. A post-bronchodilator PFT will be performed 30 minutes after the administration of Ipratropium. If a patient cannot perform an inhalation, the SABA or SAMA can be nebulized. Pulmonary function tests should be	

Section Number and Title	Old Text	New Text	Rationale for Change
		performed 30 minutes after finalization of nebulization If a patient used SABA in the first assessment of PFTs, the same SABA and mode of administration should be used in subsequent assessments. If a patient used SAMA in the first assessment of PFTs, the SAMA and mode of administration should be used in subsequent assessments	
7.2.3 Neutrophil Elastase Concentration-Sputum	Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6).	Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6).	Revised to add Visit 3 to the visits during which sputum collection is required: **Justification:** Inconsistency was noted between the section of the Protocol and Table 6: Schedule of Events
7.3.1 Leicester Cough Questionnaire	A hard copy of the LCQ will be provided separately		Only electronic copies will be provided.
7.3.2 St George's Respiratory Questionnaire	A hard copy of the SGRQ will be provided separately		Only electronic copies will be provided.
7.3.3 Neutrophil Elastase Concentration-Blood	Blood samples will be collected at ~~Screening (Visit 1),~~ Baseline (Visit 2), and Visits 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6). Detailed instruction for the blood sample collection, processing and shipment will be provided in the site study binder.	Blood samples will be collected at Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6). Detailed instruction for the blood sample collection, processing and shipment will be provided in the site study binder.	Section revised to correct the inconsistency noted between this section of the Protocol and Table 6: Schedule of Events.

Section Number and Title	Old Text	New Text	Rationale for Change
7.3.5 Inflammatory Biomarker Levels-Sputum	Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6). Only NE, proteinase 3, and cathepsin G will be analyzed	Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6). Only NE, proteinase 3, and cathepsin G will be analyzed	Visit 3 added to the visits during which sputum collection is required: **Justification:** Inconsistency was noted between the section of the Protocol and Table 6: Schedule of Events
7.3.6 Inflammatory and Tissue Degradation Biomarker Levels-Blood and Urine	Blood and urine samples will be collected at ~~Screening (Visit 1),~~ Baseline (Visit 2), and Visits 4, 6, 9, and 10 for measurement of inflammatory and tissue degradation biomarkers (refer to Table 6).	Blood and urine samples will be collected at Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of inflammatory and tissue degradation biomarkers (refer to Table 6).	Inconsistency was noted between the section of the Protocol and Table 6: Schedule of Events
8.4.1 Period of Observation for Adverse Events	For the purposes of this study, the period of observation for collection of all AEs will be from the time the subject signs the ICF ~~until 30 days after the final dose of study drug.~~	For the purposes of this study, the period of observation for collection of all AEs will be from the time the subject signs the ICF until the resolution or stabilization of the adverse events.	Section revised to clarify that patients should remain under observation until the resolution or consolidation of the adverse effects. Database lock will occur at the designated times, but follow-up of adverse events will continue until resolution or stabilization.
Synopsis: Statistical Methods 9.1 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 10mg and 25mg) 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	Details added to clarify the assumption behind the sample size calculation.

Section Number and Title	Old Text	New Text	Rationale for Change
		sample size calculation is ln(0.624)/ln(0.446)=0.584.	
9.5.1.1 Efficacy Analysis		The overall significance level is set at a one-sided 0.10 to demonstrate the superiority of INS1007 to placebo. The first step is to test INS1007 25 mg against placebo at the one-sided 0.10 level for the primary analysis and if statistically significant, INS1007 10mg will be tested against placebo at the one-sided 0.05 level for the primary analysis. If INS1007 25mg is not statistically significant against placebo for the primary analysis, no further hypothesis testing will be conducted. If only INS1007 25mg is statistically significant against placebo for the primary analysis, then the four secondary endpoints at the INS1007 25mg dose will be tested 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 both doses are statistically significant against placebo for the primary analysis, then the four secondary endpoints at the INS1007 25 mg dose will be tested 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 and the four secondary endpoints at the INS1007 10 mg dose will be tested 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.	Details added to explain the type I error techniques.

Section Number and Title	Old Text	New Text	Rationale for Change
		Type I error will not be controlled for the exploratory endpoints, the p-values produced for exploratory endpoints will be considered descriptive and hypothesis generating.	
9.5.1.2 Primary Endpoint Analysis	The primary efficacy endpoint is the time to the first pulmonary exacerbation over the 24-week treatment period. The treatment comparison will be made using the stratified log rank test for the ITT population. The time to the first exacerbation will also be analyzed using Cox regression model to estimate hazards ratio.	The primary efficacy endpoint is the time to the first pulmonary exacerbation over the 24-week treatment period. Any pulmonary exacerbation in the study between Visits 2 through 10 will be accounted for in the primary endpoint, regardless of whether it was associated with a scheduled or unscheduled visit. The treatment comparison will be made using the stratified log rank test for the ITT population. The time to the first exacerbation will also be analyzed using Cox regression model to estimate hazards ratio.	Details added for clarification.
9.7 Sample Size Reassessment		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 subjects with an event, or 61 subjects with an event, 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 subjects with an event once 70% (n=168) of the randomized subjects on trial have completed study treatment, 61 is the number of subjects with an event that was expected to have occurred once 70% of the	Details added for clarification.

<table>
<tr><th>Section
Number and Title</th><th>Old Text</th><th>New Text</th><th>Rationale for Change</th></tr>
<tr><td></td><td></td><td>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.</td><td></td></tr>
<tr><td>Appendix 4: Intense Pharmacokinetic Sampling Scheme</td><td>Intense PK Sub-Study Blood Sampling Times and Time Windows<table><tr><th>Visit</th><th>Collection Time Relative to Drug Administration</th><th>Collection Window</th></tr><tr><td>Visit ~~1~~</td><td>0 hour (pre-dose)</td><td>-30 min</td></tr></table></td><td>Intense PK Sub-Study Blood Sampling Times and Time Windows<table><tr><th>Visit</th><th>Collection Time Relative to Drug Administration</th><th>Collection Window</th></tr><tr><td>Visit 2</td><td>0 hour (pre-dose)</td><td>-30 min</td></tr></table></td><td>Justification: Inconsistency was corrected.</td></tr>
<tr><td>Multiple Locations Throughout the Protocol</td><td>Style, format, and typographical edits</td><td>Style, format, and typographical edits</td><td>Corrected any spelling errors, removed/added punctuation marks and spaces, added/used abbreviations consistently, and deleted/revised/added phrases to ensure stylistic consistency throughout the document.</td></tr>
</table>

PROTOCOL SYNOPSIS

Name of Sponsor: Insmed Incorporated

Protocol Number: INS1007-201

Name of Investigational Product: INS1007

Name of Active Ingredient: (2S)-N-{(1S)-1-cyano-2-[4-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl) phenyl] ethyl}-1,4-oxazepane-2-carboxamide

Study 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.

Study Phase: 2

Indication Under Investigation: Non-cystic fibrosis bronchiectasis

Study Objectives:

Primary Objective:

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

Secondary Objectives:

1. 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.
2. To evaluate the effect of INS1007 compared with placebo on lung function, as measured by forced expiratory volume in 1 second (FEV_1), over the 24-week treatment period.
3. 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.
4. To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period.

Exploratory Objectives:

1. 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.
2. 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.
3. 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.

4. 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, and 28.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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) at Weeks 2, 4, 12, 24, and 28.
10. 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.
11. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (forced vital capacity [FVC]) over the 24-week treatment period.
12. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (peak expiratory flow rate [PEFR]) over the 24-week treatment period.
13. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (FEF_{25-75}) over the 24-week treatment period.
14. 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.
15. To evaluate the effect of INS1007 compared with placebo on the number of exacerbations per subject over the 24-week treatment period.
16. To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by Bronchiectasis Severity Index (BSI) score at baseline, over the 24-week treatment period.
17. To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pseudomonas aeruginosa* (*Pa*) at Screening, over the 24-week treatment period.

18. 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.
19. To evaluate the effect of INS1007 compared with placebo on hospitalizations for pulmonary exacerbations over the 24-week treatment period.
20. To assess the correlations among inflammatory and tissue degradation biomarkers, concentration of active NE in blood, sputum, and urine and efficacy measures.

Safety Objective

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

Pharmacokinetic Objectives:

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

Study Design:

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 once daily (QD) for 24 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFBE).

This multi-center study will be conducted at approximately 120 sites; enrollment is competitive across all sites. Across these sites, it is planned to randomize approximately 240 subjects with NCFBE. 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.

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, and pulmonary function test (PFT) will be conducted. Subjects whose past chest radiographic image records are not available will undergo a chest computed tomography scan during Screening (Visit 1). Periodontal examination and dental cleaning procedures for inclusion should be performed prior to randomization. Subjects who meet all the inclusion but none of the exclusion criteria, except for the dental exclusion criteria, will proceed to have a dental examination for dental criteria screening. Subjects who meet all eligibility criteria will undergo a periodontal cleaning procedure prior to randomization.

Subjects will be randomized at Visit 2 (Day 1) and return thereafter for study visits at 2 (Visit 3), 4 (Visit 4), 8 (Visit 5), 12 (Visit 6), 16 (Visit 7), 20 (Visit 8), 24 (Visit 9) and 28 (Visit 10) weeks. There will be a visit window of ± 3 days for each of the scheduled visits. During each visit, all assessments and procedures will be performed as described in Section 6 of this protocol. Study treatment will occur between Visits 2 and 9.

Subjects will be required to have an end-of-study (EOS) visit (Visit 10) at Week 28 to collect blood, sputum, and urine samples for biomarker assessment and pregnancy test for WOCBP 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.

Pharmacokinetic Sub-study:

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 (see Section 7.6.1). Pharmacokinetic samples will be analyzed in batches on an ongoing basis.

Study Population:

Approximately 240 subjects diagnosed with NCFBE will be randomized.

Treatment Duration:

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 EOS (Visit 10).

Subject Eligibility Criteria:

Inclusion Criteria:

Subjects who have given their signed, informed consent, are male or female between 18 and 85 years of age (inclusive) with a body mass index > 18.5 at Screening (Visit 1) and have a clinical history consistent with NCFBE will be eligible for enrollment in the study.

For more comprehensive details of the inclusion criteria refer to Section 4.1.1 of this protocol.

Exclusion Criteria:

Subjects who have a primary diagnosis of chronic obstructive pulmonary disease or asthma, have bronchiectasis due to cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, or α1-antitrypsin deficiency, are current smokers as defined per Centers for Disease Control and Prevention criteria, or currently being treated for a nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis will not be eligible for enrollment in the study.

For more comprehensive details of the exclusion criteria refer to Section 4.1.2 of this protocol.

Drug Product, Strength, Dosage Form, and Route of Administration:

The study drugs (INS1007 and placebo) will be supplied by the Sponsor.

Product Name	Product Strength	Dosage Form	Route and Frequency of Administration
INS1007	10 mg	round, biconvex, brown, film coated tablet	Orally, once daily before breakfast
INS1007	25 mg	round biconvex, brown, film coated tablet	Orally, once daily before breakfast
Placebo	No active ingredient	round, biconvex, brown, film coated tablet	Orally, once daily before breakfast

Study Endpoints:

Primary Endpoint:

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

Pulmonary exacerbation definition. 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.

Secondary Endpoints:

1. Change from Baseline in QOL-B Respiratory Symptoms Domain score over the 24-week treatment period
2. Change from Screening in post-bronchodilator FEV_1 over the 24-week treatment period
3. Change in concentration of active NE in sputum from pre-treatment to on-treatment
4. Rate of pulmonary exacerbations (number of events per person-time) over the 24-week treatment period

Exploratory Endpoints:

1. Change from Baseline in QOL-B scores (all domains excluding the 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 in concentration of active NE in sputum from pre-treatment to Weeks 2, 4, and 28
5. Change in concentration of active NE in reagent-stimulated blood from pre-treatment to Weeks 2, 4, 12, 24, and 28
6. Change from Baseline in sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28
7. Change in concentration of active NE in sputum (stratified by sputum color) at baseline from pre-treatment to Weeks 2, 4, 12, and 28

8. Change from Baseline in inflammatory and tissue degradation biomarker levels in sputum (the biomarkers which may be assessed are eg, proteinase 3 and cathepsin G) at Weeks 2, 4, 12, 24, and 28
9. Change from Baseline in inflammatory and tissue degradation biomarker levels in blood (biomarkers which may be assessed are eg, ANC, proteinase 3, and cathepsin G) at Weeks 2, 4, 12, 24, and 28
10. Change from Baseline in tissue degradation marker level in urine (desmosine) at Weeks 2, 4, 12, 24, and 28
11. Change from Screening in FVC at Weeks 12 and 24
12. Change from Screening in PEFR at Weeks 12 and 24
13. Change from Screening in FEF_{25-75} at Weeks 12 and 24
14. Total duration (in days) of exacerbations, per subject, over the 24-week treatment period
15. Total number of exacerbations per subject over the 24-week treatment period
16. Time to first pulmonary exacerbation, exacerbation rate, QOL measures, and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by BSI score at baseline, over the 24-week treatment period
17. Time to first pulmonary exacerbation, exacerbation rate, QOL measures, and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pa* at Screening, over the 24-week treatment period
18. Frequency of use of rescue medications (rescue medications include SABAs, SAMAs, newly prescribed LABAs, LAMAs, and oxygen) over the 24-week treatment period
19. Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period
20. Descriptive assessment of the change in inflammatory and tissue degradation biomarkers and concentration of active NE in blood, sputum, and urine, over the 24-week treatment period

Safety Endpoints:

The safety endpoints will include AEs, 12-lead ECG measurements, clinical laboratory testing results, vital sign measurements, physical examination results, and PFT measurements. Adverse events of special interest that will be reported include hyperkeratosis, periodontitis/gingivitis, and other infections.

Pharmacokinetic Endpoints:

The PK parameters, as estimated using non-compartmental analysis methods, will include maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), average plasma concentration at steady state (C_{ss}), maximum plasma concentration at steady state ($C_{max,ss}$), time to maximum plasma concentration at steady state ($t_{max,ss}$), minimum plasma concentration at steady state (C_{minss}), and area under the plasma concentration curve from 0 to 8 hours (AUC_{0-8}).

Statistical Methods:

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, assuming10% of the subjects will discontinue study drug before completing 24 weeks of treatment.

Efficacy Analysis

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

The efficacy analysis of the time to the first exacerbation will be performed for the intent-to-treat (ITT) population using Kaplan Meier curves. The treatment comparison will be made using the stratified log rank test for the ITT population. The time to the first exacerbation will also be analyzed using Cox regression model to estimate hazards ratio.

A supportive analysis of the primary efficacy endpoint will be performed for the per-protocol population using the same methods as for the ITT population. The exacerbation rate will be analyzed for the ITT population stratified by *Pa* colonization status and maintenance use of macrolides at Baseline.

Secondary endpoints of QOL-B, FEV_1, and NE will be analyzed using analysis of variance; the rate of pulmonary exacerbations will be analyzed using Cochran-Mantel-Haenszel statistics.

Safety Analysis

Subject disposition will be listed and summarized including the number of withdrawals and the primary reason for withdrawal. Subjects excluded from any analysis sets will be listed including the reasons for exclusions.

All safety data will be listed for each subject and summarized appropriately. Adverse events will be coded using the Medical Dictionary for Regulatory Activities and summarized by system organ class and preferred term. Additional summaries by severity and relationship to study treatment will be presented.

All clinical safety laboratory data and vital signs will be listed and summarized including changes from Baseline. Any out of range laboratory measurements will be flagged in the listings.

Digital ECG (dECG) data will be smoothed, and the heart rate (HR) and corrected QT interval by Fridericia (QTcF) will be derived from the smoothed data at each time point. The dECG data will be listed and summarized descriptively; outlier analyses for QTcF will also be performed.

Pharmacokinetic Analysis

For subjects participating in the PK sub-study, plasma concentrations of INS1007 will be listed and summarized by dose level of INS1007 over each scheduled sampling time using descriptive statistics, as appropriate. Individual plasma concentration data versus time will be presented in data listings, along with graphical plots of individual and geometric mean plasma concentration-time plots presented in linear and semi-logarithmic scale. Plasma PK parameters will be summarized using descriptive statistics, as appropriate.

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. Actual sampling times and INS1007 plasma concentrations will be listed but not summarized.

Plasma concentration data for INS1007 will be pooled with corresponding data from other Sponsor studies for population PK (PPK) modelling. The methods and results of any PPK analyses will be described and reported separately.

Pharmacodynamic Analysis

The NE activity in sputum and blood will be calculated as percent inhibition from the pre-treatment activity and normalized by ANC (blood only). Pre-treatment value is defined as the mean value of NE activities at Screening and Baseline and will be listed and summarized together with the ANC measurements.

All other biomarker levels at pre- and post-dose levels will be listed and summarized.

Plasma concentration data for INS1007 will be pooled with corresponding data from other studies for population PK/PD modelling of the exposure response relationship. The methods and results of any population PK/PD analyses will be described and reported separately.

Data Monitoring Committee:

An independent, external Data Monitoring Committee (DMC), comprised of at least 2 physicians with pulmonary expertise, an expert in periodontal disease, an expert in dermatology, and a statistician who is experienced in the evaluation of clinical safety data will be set up to review all AEs and serious AEs to ensure the safety of subjects enrolled into this study. Additional members may be added by the DMC if it is determined that additional expertise is required to evaluate the clinical safety data. The DMC members will review the data in a semi-blinded or un-blinded manner at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review those data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. Further details of the DMC will be provided separately in the DMC charter.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Code of Federal Regulations Title 21
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AST	aspartate aminotransferase (SGOT)
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
AUC_{0-8}	area under the plasma concentration-time curve from 0 to 8 hours
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BMI	body mass index
BP	blood pressure
BSI	Bronchiectasis Severity Index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
C_{max}	maximum plasma concentration of drug
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,ss}$	minimum plasma concentration at steady state
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
C_{ss}	average plasma concentration at steady state
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DMC	Data Monitoring Committee
dECG	digital ECG
DPP1	dipeptidyl peptidase 1
ECG	electrocardiogram
eCRF/CRF	(electronic) case report form

Abbreviation	Definition
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
ERS	European Thoracic Society
FDA	Food and Drug Administration
FEF_{25-75}	forced expiratory flow between 25% and 75% of forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
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 Council for Harmonisation
IEC	Independent Ethics Committee
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IL-8	onterleukin-8
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
LABA	long-acting beta agonist
LAM	lactational amenorrhea method
LAMA	long-acting muscarinic antagonist
LCQ	Leicester Cough Questionnaire
LTB4	leukotriene B4
MAD	multiple ascending dose
MCP-1	monocyte chemotactic protein 1 (CCL2)
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NCFBE	non-cystic fibrosis bronchiectasis
NCI	National Cancer Institute
NE	neutrophil elastase
NOAEL	no-observed-adverse-effect level
NSP	neutrophil serine proteinase
PD	pharmacodynamic(s)
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PI	Principal Investigator
PK	pharmacokinetic(s)
PLS	Papillon-Lefèvre Syndrome
PP	per protocol
PPK	population PK
PRO	patient-reported outcome
QD	once daily
QOL	quality of life
QOL-B	Quality of Life Questionnaire-Bronchiectasis
QTcF	corrected QT interval by Fridericia
RANTES	regulated on activation, normal T-cell expressed and secreted
RTSM	randomization and trial supply management
SABA	short-acting beta agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SAP	statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
SSRI	selective serotonin receptor inhibitor
T	body temperature
T3	triiodothyronine
T4	thyroxine
TBL	total bilirubin
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration

Abbreviation	Definition
$t_{max,ss}$	time to maximum plasma concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WOCBP	women of child bearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Investigational Product(s)

1.1.1. Name

The chemical name of INS1007 is (2S)-N-{(1S)-1-cyano-2- [4-(3-methyl-2-oxo-2,3-dihydro- 1,3-benzoxazol-5-yl) phenyl] ethyl}-1,4-oxazepane-2-carboxamide.

1.1.2. Description

INS1007 is a potent, selective, competitive, and reversible dipeptidyl peptidase I (DPP1, also known as cathepsin C) inhibitor that was shown to inhibit the formation of all 3 active neutrophil serine proteinases (NSPs) in maturing neutrophils *in vitro* and *in vivo*.

1.1.3. Intended Use Under Investigation

INS1007 is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFBE).

1.2. Disease Background

Bronchiectasis is a disease characterized by localized, irreversible enlargement of bronchi and bronchioles that may lead to obstructed breathing caused by abnormal mucus production. Bronchiectasis symptoms typically include a chronic dry or wet cough. Other symptoms include shortness of breath, coughing up blood, and chest pain. Wheezing and nail clubbing may also occur. People with the disease often get frequent lung infections.

Bronchiectasis, along with chronic obstructive pulmonary disease (COPD), acute lung injury, acute respiratory distress syndrome, and cystic fibrosis (CF) are all conditions of severe pulmonary dysfunction resulting from a massive inflammatory response. The histological characteristic of all these inflammatory lung diseases is the accumulation of neutrophils in the interstitium and alveoli of the lung. Their activation leads to the release of multiple cytotoxic products including reactive oxygen species and proteases (serine, cysteine, and metalloproteases).

Neutrophils contain 4 main types of granules: azurophilic or primary granules, specific or secondary granules, gelatinase or tertiary granules, and secretory granules. Azurophilic granules are believed to be the first to form during neutrophil maturation in the bone marrow and are characterized by the expression of related NSPs: neutrophil elastase (NE), proteinase 3, and cathepsin G. The lysosomal cysteine DPP1 is the proteinase that activates these 3 NSPs by removal of the N-terminal dipeptide sequences from their precursors during azurophilic granule assembly (Pham et al, 2004). Dipeptidyl peptidase 1 is broadly expressed in tissues but is highly expressed in cells of hematopoietic lineage such as neutrophils.

The 3 NSPs act in combination with reactive oxygen species to help degrade engulfed microorganisms inside phagolysosomes. The NSPs are also abundantly secreted into the extracellular environment upon neutrophil activation at inflammatory sites. A fraction of the released proteases remains bound in an active form on the external surface of the plasma membrane so that both soluble and membrane-bound NSPs can regulate the activities of a variety of chemokines, cytokines, growth factors, and cell surface receptors by either converting them to

active forms or degrading them by proteolytic cleavage. Secreted proteases can stimulate mucus secretion and inhibit mucociliary clearance, but also activate lymphocytes and cleave apoptotic and adhesion molecules (Bank and Ansorge, 2001; Meyer-Hoffert et al, 2009; Pham et al, 2006; Voynow et al, 2008). Thus, they possess pro- and anti-inflammatory activities at sites of inflammation.

The physiological balance between proteases and anti-proteases is required for the maintenance of the lung's connective tissue, and an imbalance in favor of proteases can result in lung injury (Tetley, 1993; Umeki et al, 1988). Because of roles of NSPs in inflammation, they are potential therapeutic targets for chronic inflammatory lung diseases such as bronchiectasis.

INS1007 is a potent, selective, competitive, and reversible inhibitor of DPP1 that is currently being developed for the treatment of NCFBE. It is hypothesized that INS1007 will have beneficial effects via decreasing inflammation and mucus hypersecretion, which will in turn lead to a decrease in pulmonary exacerbation and an improvement in lung function (cough, sputum production, and forced expiratory volume in 1 second [FEV_1]) in NCFBE subjects. There is also a potential benefit with INS1007 for modifying NCFBE progression by reducing the accelerated rate of lung function decline or lung tissue destruction.

Subjects having NCFBE experience pulmonary exacerbations with an average frequency ranging from 1.5 to 6 per year (Chalmers et al, 2014; Goeminne et al, 2014; Kelly et al, 2003). Currently, there is no standard of care for prophylactic pharmacological treatment of NCFBE. The primary goal of treatment is to treat the underlying cause, prevent disease progression, maintain or improve lung function, and improve the symptoms and quality of life (QOL).

There is currently no therapy approved by regulatory authorities in the United States (US) or Europe for the treatment of NCFBE.

1.3. Development Program

1.3.1. Nonclinical Studies

INS1007 is a reversible, competitive inhibitor of DPP1, with high potency as measured *in vitro* using isolated human DPP1 enzyme and a hematopoietic cell line known to express DPP1. Human primary neutrophil studies demonstrated that INS1007 significantly inhibits the activation of NSPs, resulting in decreased elastolytic ability of the cells *in vitro*. Studies with naïve and lipopolysaccharide-induced pulmonary inflammation models in the rat showed that DPP1 inhibition with oral INS1007 translates well *in vivo* as significant decreases in the activities of NSPs were observed.

The secondary and safety pharmacology of INS1007 were investigated using both *in vitro* and *in vivo* models. In the *in vitro* model, the concentration of the drug causing a half-maximal inhibitory effect (IC50) on the human *ether-a-go-go* related gene (hERG)-encoded potassium channel was 13.9 µM. In a single-dose cardiovascular telemetry study in dogs, transient effects were seen on heart rate (HR), mean diastolic blood pressure (BP), mean BP, QA interval, and-QT-interval corrected for HR. Based on the results of the telemetered dog study with a no-observed-adverse-effect level (NOAEL) of 50 mg/kg and a clinical dose of 25 mg, the safety margin derived from the maximum observed concentration (C_{max}) in plasma is 44 (for free

INS1007) and 19 (for total INS1007), indicating a low level of concern for cardiovascular effects.

No effect was observed on either the central nervous or respiratory systems in rats.

Details of nonclinical pharmacokinetic (PK), drug metabolism, and toxicology studies can be found in the current INS1007 Investigator's Brochure (IB).

1.3.2. Clinical Experience

INS1007 has been assessed in 2 healthy volunteer studies (D6190C00001 and D6190C00003).

Study D6190C00001

Study D6190C00001 was a Phase 1, randomized, single-blind, placebo-controlled, multi-part study in healthy adult male volunteers.

Part 1a was a single ascending dose (SAD) study in which 45 subjects received either placebo (15 subjects) or INS1007 (5, 15, 35, 50, or 65 mg [6 subjects per dose level]) under fasting conditions.

Part 1b was a single-dose food effect study in which 8 subjects (Cohort 3 from Part 1a after a washout of at least 7 days) received either placebo (3 subjects) or 35 mg INS1007 (5 subjects) after a high-fat breakfast.

Part 2 was a multiple ascending dose (MAD) study in which 36 subjects (who did not participate in Part 1) received either placebo (12 subjects) or INS1007 (6 subjects received 10 mg/day for 21 days, 8 subjects received 25 mg/day for 28 days, and 10 subjects received 40 mg/day for 28 days) under fasting conditions.

The safety variables for INS1007 were adverse events (AEs); safety laboratory assessments (hematology, clinical chemistry, urinalysis); vital signs (pulse rate, BP, oral body temperature [T]); 12-lead paper and digital electrocardiogram (ECG, pre-hospital ECG, and digital ECG [dECG]); telemetry; physical examination results (including evaluation of gingiva and teeth, and evaluation of palms and soles). In addition, part 2 laboratory assessments also included neutrophil phagocytosis, oxidative burst, spermatogram [fertile male subjects participating in Cohort 3 and onward] and reproductive hormones [Cohort 3 and onward]).

Study D6190C00003

Study D6190C00003 was an open-label, fixed sequence, 3-period, drug-drug interaction (DDI) study of the effects of concomitant verapamil (moderate CYP3A4 inhibitor) and itraconazole (strong CYP3A4 inhibitor) on the single-dose PK of INS1007 and its tolerability and safety in healthy adult male volunteers. The study consisted of 3 periods with at least a 7-day washout between Periods 1 and 2 and at least a 14-day washout between Periods 2 and 3. During Period 1, 15 subjects received a single dose of INS1007 (25 mg). During Period 2, the same subjects received verapamil (240 mg, extended release formulation) on Days 1 through 10 plus a single dose of INS1007 (25 mg) on Day 5. During Period 3, the same subjects received itraconazole (200 mg as oral solution of 10 mg/mL) twice on Day 1 and then once daily (QD) on Days 2 through 11 plus a single dose of INS1007 (25 mg) on Day 6. All drugs were administered under fasting conditions.

Safety variables included AEs, vital signs (systolic and diastolic BP, pulse rate and temperature), electrocardiograms (ECGs, safety, and dECGs), laboratory assessments (hematology, clinical chemistry, and urinalysis) and physical examinations (including evaluation of gingiva and teeth, and evaluation of palms and soles). Viral serology, tuberculosis (TB) screen and urine drugs of abuse, alcohol, and cotinine were assessed for eligibility. The use of concomitant medications was also assessed and reported.

In both studies, INS1007 was well tolerated in humans up to the highest dose levels assessed (single dose of 65 mg and multiple dose of 40 mg/day for 28 days). All treatment-emergent adverse events (TEAEs) in the Phase 1 studies were mild or moderate. None of the reported TEAEs were severe. In both studies, the most common TEAE was headache (generally mild and considered related to the study treatment). No subject died during the study and no subject experienced a serious adverse event (SAE). Treatment discontinuation due to a TEAE was rare. One subject in Study D6190C0001 discontinued 25 mg/day INS1007 on Day 13 of a planned 28-day treatment period due to an AE of drug eruption lichen, planus-like.

Papillon-Lefèvre Syndrome (PLS) is a rare disease characterized by profound deficiency of DPP1. The sequelae of this disease are of relevance and importance for assessment in the development program for INS1007. The 2 primary clinical manifestations in PLS subjects who exhibit a spectrum of decreased DPP1 activity due to mutations in the DPP1 gene are palmoplantar keratinization, characterized by redness and thickening of the soles and palms, and periodontal disease, which can be serious and can affect both primary and permanent teeth. As DPP1 is the enzyme inhibited by INS1007, AEs of the gingiva and skin of the palms and soles were of special interest in INS1007 Phase 1 clinical studies. Mild gingival bleeding was observed in both subjects taking INS1007 and those taking placebo with no obvious difference between active and placebo treatments. Mild skin and subcutaneous tissue disorders were observed in subjects on INS1007.

No trends were observed in clinical laboratory results, 12-lead ECGs, telemetry, physical examination, or spermatogram results. Abnormal findings observed in vital signs were not considered to be clinically significant. Details of PK studies can be found in the INS1007 IB.

1.3.3. Clinical Pharmacokinetics

Pharmacokinetic analyses of the first-in-human Phase 1 clinical study of INS1007 in healthy subjects (D6190C00001) indicates that INS1007 exhibits relatively fast oral absorption with a time to maximum plasma concentration (t_{max}) generally observed between 0.5 to 1.5 hours after dosing. INS1007 also presented dose-proportional steady state exposures around the anticipated therapeutic range of 10 to 25 mg. INS1007 has a mean apparent terminal elimination half-life ($T_{1/2}$) of approximately 25 to 30 hours resulting in accumulation in plasma (2.3 to 2.5 and 1.7 to 1.9-fold accumulation for AUC and C_{max}, respectively). Excretion of INS1007 in urine is moderate (11% to 20% of dose) following a single dose. Food effect data indicate that administration of a single 35 mg dose of INS1007 following a high-fat breakfast results in a delayed absorption of 3.25 hours, and decreased C_{max} of 36% compared to fasting. The effect of food on AUC is low, with a decrease of 9%.

The primary isozymes responsible for Phase 1 metabolism of INS1007 are the cytochrome P450 (CYP) 3A4/5, and to a lesser extent CYP2C8 and CYP2D6. No unique human metabolites have been identified to date. The *ex-vivo* plasma protein binding of INS1007 in human plasma was

concentration-independent at clinically relevant concentrations (0.1 to 100 µmol/L) and is estimated to be 87.2%.

Because the clearance of INS1007 is predicted to include significant involvement of CYP3A4 and CYP3A5, a drug-drug interaction clinical study of INS1007 (D6190C00003) was conducted to investigate the effect of verapamil, a moderate CYP3A4/5 inhibitor, and itraconazole, a strong CYP3A4/5 inhibitor, on the PK of INS1007. INS1007 C_{max} and AUC were not bioequivalent with co-administration of verapamil compared to INS1007 administration alone, with 53% (90% CI = 136, 173) and 32% (90% CI = 122, 144) increases, respectively. INS1007 AUC was bioequivalent after co-administration with itraconazole compared to INS1007 alone (90% CI = 105, 123), however, C_{max} was significantly decreased by 39% (90% CI = 54, 68). Results for itraconazole demonstrate that there is no clinically relevant safety concern when co-administration INS1007 with strong CYP3A4/5 inhibitors. However, verapamil results indicate that other non-CYP-related pathways may be at play and that further *in vitro* investigations to elucidate the mechanism of the verapamil drug-drug interaction are warranted.

INS1007 does not inhibit any of the major CYP enzymes in *in vitro* CYP inhibition experiments (up to 30 µmol/L). The geometric mean steady state total C_{max} in healthy subjects from study D6190C00001 at 25 mg QD (the highest dose planned in the present study) was 0.598 µmol/L (C_{max}, u = 0.077 µmol/L). Based on the dose and regimen planned to be investigated in this study in NCFBE subjects, INS1007 plasma concentrations are unlikely to be in the range that would inhibit these CYP enzymes ([I]/Ki ratio <0.1), and therefore unlikely to precipitate a significant drug-drug interaction (DDI) via CYP inhibition when co-administered with other agents that are substrates for CYP enzymes.

In vitro studies indicate that INS1007 is not a time-dependent inhibitor and has low risk of being a perpetrator of transporter-mediated drug-drug interactions via OATP1B1, BCRP or P-gp. Although INS1007 is a weak inducer of CYP3A4 and CYP2B6 mRNA *in vitro*, data in healthy subjects from study D6190C00001 appeared to indicate a time-dependent increase in plasma AUC by 52% to 59% at the 10, 25 and 40 mg dose levels. These results are not consistent with induction of CYP3A4, and the observed increase is thought to be due to a high degree of extrapolation in the Day 1 AUC estimates. For this reason, the time invariance for INS1007 cannot be ruled out.

1.4. Study Rationale

INS1007 is a potent, selective, competitive and reversible DPP1 inhibitor that was shown to inhibit the formation of all 3 active NSPs in maturing neutrophils *in vitro* and *in vivo*.

Activation of the 3 NSPs in the maturing neutrophils occurs via removal of a dipeptide from their precursors by the lysosomal cysteine DPP1/cathepsin C (Adkison et al, 2002; Pham et al, 1999). Dipeptidyl peptidase 1 is broadly expressed in tissues but is particularly highly expressed in cells of hematopoietic lineage such as neutrophils. Neutrophils contain 4 main types of granules: azurophil or primary granules, specific or secondary granules, gelatinase or tertiary granules and secretory granules. Azurophil granules are believed to be the first to form during the neutrophil maturation in the bone marrow and are characterized by the expression of the related (neutrophil) serine proteases of NE, proteinase 3 and cathepsin G. Dipeptidyl peptidase 1 alone activates these proteases by removing the N-terminal dipeptide sequences during azurophil granule assembly (Korkmaz et al, 2010; Pham et al, 2004).

It is hypothesized that the functional inhibition of NSPs by a DPP1 inhibitor such as INS1007 will decrease inflammation and mucus hypersecretion, leading to slowing down lung tissue destruction, and decreasing the exacerbation rate in subjects with neutrophilic lung conditions with a protease-driven pathology (Root et al, 2016) such as NCFBE.

This study will evaluate whether this hypothesis is confirmed.

1.5. Risks and Benefits for Study Subjects

1.5.1. Potential Benefits

The effects of n NE on airway epithelial cells includes slowing of ciliary beat frequency and promotion of mucus hypersecretion (Amitani et al, 1991; Voynow et al, 1999) while impairment of opsonophagocytosis occurs at multiple levels (Tosi et al, 1990). In a recent proof of concept study, inhibition of NE demonstrated promising signals in COPD subjects with current symptoms of chronic bronchitis. In this 3-month study with AZD9668 (a NE inhibitor) conducted by AstraZeneca, an improvement in FEV_1 (both pre- and post-bronchodilator) was observed in subjects with a BCSS score for cough and/or sputum of ≥ 2 (Kuna, 2012). This FEV_1 improvement was noted within a few weeks of dosing and was approximately 100 mL in magnitude (versus placebo).

It is postulated that administration of INS1007 may result in beneficial effects for patients suffering from NCFBE via decreasing inflammation and mucus hypersecretion, leading to an improvement in respiratory symptoms (eg, cough and sputum production) and lung function (eg, FEV_1) and a decrease in exacerbation rate. Since INS1007 acts upstream of NE and inhibits 2 other NSPs regulated by DPP1, it may have a larger impact on slowing lung damage progression in NCFBE patients compared to inhibition of NE alone.

1.5.2. Risks and Risk Mitigation Strategies

1.5.2.1. Hyperkeratosis/Periodontitis

Many PLS patients experience diffuse palmoplantar keratosis and severe periodontitis, leading to premature loss of both the deciduous and permanent teeth (Korkmaz et al, 2010). Because INS1007 inhibits DPP1, the enzyme that PLS patients lack, these sequelae were of interest in the 2 Phase 1 studies for INS1007.

In Part 2, the MAD phase, of Study D6190C0001, 2 healthy subjects who received 25 mg of INS1007 experienced dermatological events: 1 subject was diagnosed to have a lichenoid drug reaction which was considered possibly related to INS1007 by the Investigator and resolved after INS1007 administration was stopped. The subject had previously experienced a similar type of event in another clinical study. In the second subject, skin exfoliation was noticed in the volar site at the base of the fingers, and the event resolved 9 days after INS1007 administration was stopped. It is the study Sponsor's thought that there was a reasonable possibility of a causal relationship between this event and INS1007.

Dental lesions/periodontitis were observed in the INS1007 6-month dog toxicity study in the highest dose group (147 and 63-fold higher exposure than the highest dose planned for this study based on free and total INS1007, respectively). In the mid-dose group of this 6-month dog toxicity study, no dental lesions/periodontitis were observed (21 and 9-fold higher exposure than

the highest dose planned for this study based on free and total INS1007, respectively). In Part 2, MAD, of Study D6190C0001, 3 subjects who received INS1007 and 1 subject who received placebo experienced gingival bleeding that were all mild in intensity.

Entry criteria and monitoring procedures have been incorporated into the study design to avoid impairing the ability of the study to detect a potential safety signal and to mitigate against putting susceptible subjects at inappropriate risk. To specifically mitigate the risks related to skin hyperkeratosis, subjects having a history of hyperkeratosis or erythema in palms or soles will be excluded from this study. Subjects will be closely monitored throughout the study with special evaluation of the palms and soles, but also the dorsum of the hands and feet, Achilles tendon area, knees, and elbows. Subjects will be discontinued from the study administration in the case of skin thickening.

To specifically mitigate risks associated with periodontitis, subjects will undergo a dental examination during Visit 1 (Screening). Subjects who have severe periodontitis will be excluded from the study. Eligible subjects will undergo a deep dental cleaning during Screening before enrollment. During the treatment period (Visits 2 through 9), subjects' mouth, gingiva and teeth will be examined by the Principal Investigator (PI) at each visit. Should any subject have any gingiva or tooth issue or worsening of their pre-existing condition, the subject will be referred to the study-designated dentist for further evaluation. Subjects will also be examined by the study-designated dentist at Screening (Visit 1), Week 8 (Visit 5), and Week 24 (Visit 9). Subjects will be discontinued from study drug administration if they develop severe periodontitis.

1.5.2.2. Infections

Because NSPs play a direct role in neutrophil responses against invading pathogens, inhibition of NSP activation might be considered to increase the risk of infection. However, despite the severe deficiency in NSPs, there are no consistent reports of generalized immune deficiency in these PLS patients. Recent data has shown that neutrophils from most subjects with PLS displayed normal microbicidal activity against *E coli* and *S aureus*, but neutrophils from certain subjects were defective in microbial killing (Pham et al, 2004). This clinical observation suggests that NSPs were not essential antimicrobial molecules and may explain why only a few subjects with PLS demonstrated recurrent systemic infections. Based on these observations it is expected that subjects given INS1007 will have limited risk for developing infections.

Nonetheless, to minimize a potential risk, subjects with recent acute infections will be excluded from the study. Subjects will be monitored continually for signs and symptoms of any infections and will have clinical safety laboratory tests at each study visit. Subjects with an absolute neutrophil count (ANC) < 1000/mm^3 will be discontinued from the study.

All serious infections and all specific infections believed to be associated with neutropenia, such as soft tissue infection, urinary tract infection should be entered in the infection module of the electronic case report form (eCRF).

1.5.2.3. Testicular Toxicity

In dogs, testicular toxicity and periodontal disease were observed; such findings were not observed in rats. In the 1-month dog study, testicular toxicity was observed at the high dose (75 mg/kg/day), the testicular findings included swollen spermatocytes in the testes and

increased cellular debris in the epididymides which were completely reversible after a 1-month recovery period.

In the 6-month repeat-dose toxicology study in dogs at 8 and 50 mg/kg/day, dose-dependent changes in the testis and epididymis were observed. The testicular findings included swollen spermatocytes in the testes and increased cellular debris in the epididymides.

A proportion of tubules had hypospermatogenesis which represents an inefficiency of spermatogenesis in segments of some tubules. Hypospermatogenesis was considered a new finding in the high-dose group at the end of the recovery period, as it was not present at the end of the dosing period. At the end of the dosing period, little or no active spermatogenesis was present in the testes, precluding the finding of hypospermatogenesis. Following the recovery period, spermatogenesis resumed in all 3 recovery dogs with all stages of sperm development being present. However, the testes were not histologically normal, as hypospermatogenesis was present in levels above those seen in concurrent controls. This observation was possible because active spermatogenesis was present at the end of the recovery period, demonstrating recovery of the tubular degeneration/atrophy present at the end of dosing. Therefore, the recovery is described as partial.

The findings at the highest dose of 50 mg/kg/day were partially reversed at the end of the recovery period. Further details of the results in dogs in the 1 and 6-month toxicology studies can be found in the current IB. The informed consent form (ICF) for the study will describe the potential risks to the male reproductive system.

1.5.3. Conclusions on Risk-Benefit

Considering the potential benefits to subjects with NCFBE, all the available data for INS1007 from the nonclinical toxicity studies, the 2 Phase 1 studies, and the risk mitigation strategies to be put in place, this study, in the opinion of the Sponsor, is considered to have a favorable risk-benefit ratio.

1.6. Population, Route, Dosage, Dosage Regimen, Treatment Period

Subjects who have given their signed, informed consent, are male or female between 18-85 years of age (inclusive) with a Body Mass Index (BMI) >18.5 at Visit 1 (Screening) and have a clinical history consistent with NCFBE will be eligible for enrollment in the study. The goal is to randomize approximately 240 subjects diagnosed with NCFBE.

INS1007 will be provided as round, biconvex, brown, film-coated tablets in strengths of 10 mg and 25 mg to be administered orally QD for 24 weeks of treatment.

Placebo will be identical to study drug as round, biconvex, brown, film-coated tablets without active study drug and administered orally QD for 24 weeks of treatment.

2. STUDY OBJECTIVES

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

1. To evaluate the effect of INS1007 compared with placebo on QOL, as assessed by the Quality of Life Questionnaire-Bronchiectasis (QOL-B), Respiratory Symptoms Domain score, over the 24-week treatment period
2. To evaluate the effect of INS1007 compared with placebo on lung function, as measured by FEV_1, over the 24-week treatment period
3. 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 on-treatment concentration
4. To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period

2.1.3. Exploratory Objectives

1. 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
2. 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
3. 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
4. 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, and 28
5. 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
6. 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
7. 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

8. 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
9. 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) at Weeks 2, 4, 12, 24, and 28
10. 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
11. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (forced vital capacity [FVC]) over the 24-week treatment period
12. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (peak expiratory flow rate [PEFR]) over the 24-week treatment period
13. To evaluate the effect of INS1007 compared with placebo on the following pulmonary function parameters as measured by spirometry (forced expiratory flow25 to 75% [FEF_{25-75}]) over the 24-week treatment period
14. 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
15. To evaluate the effect of INS1007 compared with placebo on the number of exacerbations per subject over the 24-week treatment period
16. To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by Bronchiectasis Severity Index (BSI) score at baseline, over the 24-week treatment period
17. To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation, exacerbation rate, QOL measures and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pseudomonas aeruginosa* (*Pa*) at Screening, over the 24-week treatment period
18. 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
19. To evaluate the effect of INS1007 compared with placebo on hospitalizations for pulmonary exacerbations over the 24-week treatment period
20. To assess the correlations among inflammatory and tissue degradation biomarkers, concentration of active NE in blood, sputum, and, urine and efficacy measures

2.1.4. Safety Objective

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

2.1.5. Pharmacokinetic Objectives

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study to assess the efficacy, safety and tolerability, and PK of INS1007 administered QD for 24 weeks in subjects with 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 (see Section 7.6.1). Pharmacokinetic samples will be analyzed in batches on an ongoing basis.

Screening Period (Visit 1)

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, and PFTs will be conducted. Subjects whose past chest radiographic image records are not available will undergo a chest computed tomography (CT) scan during Screening (Visit 1). Periodontal examination and dental cleaning procedures for inclusion should be performed prior to randomization.

Treatment Period (Visits 2 Through 9)

On Day 1 (Visit 2), vital signs, and sputum and blood samples for biomarkers will be collected. 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.

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

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 Visit 3 and Visit 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.

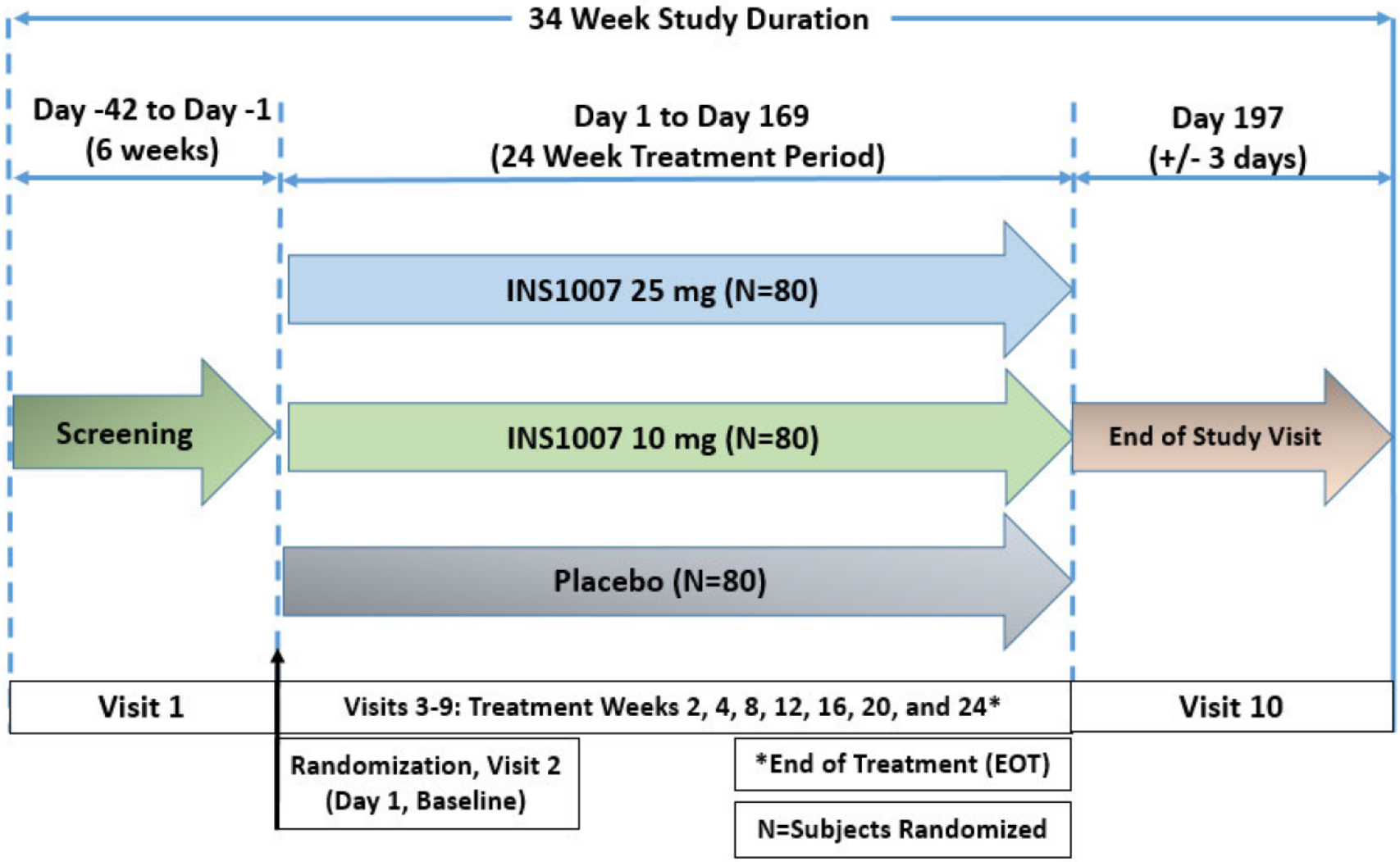
For those subjects participating in the PK sub-study, PK samples will be collected at the specified time points detailed in Section 7.6.

End-of-Study Visit (Visit 10)

Subjects will be required to have an EOS visit (Visit 10) at week 28 to collect blood, sputum, and urine samples for biomarker assessment and pregnancy test for WOCBP, and to collect information on AEs and concomitant medication 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



3.2. Study Endpoints

3.2.1. Primary Endpoint

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

Pulmonary exacerbation definition. 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.

3.2.2. Secondary Endpoints

1. Change from Baseline in QOL-B Respiratory Symptoms Domain score over the 24-week treatment period
2. Change from Screening in post-bronchodilator FEV_1 over the 24-week treatment period
3. Change in concentration of active NE in sputum from pre-treatment to on-treatment
4. Rate of pulmonary exacerbations (number of events per person-time) over the 24-week treatment period

3.2.3. Exploratory Endpoints

1. Change from Baseline in QOL-B scores (all domains excluding the 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 in concentration of active NE in sputum from pre-treatment to Weeks 2, 4, and 28
5. Change in concentration of active NE in reagent-stimulated blood from pre-treatment to Weeks 2, 4, 12, 24, and 28
6. Change from Baseline in sputum color (assessed by the sputum color chart) at Weeks 2, 4, 12, 24, and 28

7. Change in concentration of active NE in sputum (stratified by sputum color) at Baseline from pre-treatment to Weeks 2, 4, 12, and 28
8. Change from Baseline in inflammatory and tissue degradation biomarker levels in sputum (the biomarkers which may be assessed are eg, proteinase 3 and cathepsin G) at Weeks 2, 4, 12, 24, and 28
9. Change from Baseline in inflammatory and tissue degradation biomarker levels in blood (biomarkers which may be assessed are eg, ANC, proteinase 3, and cathepsin G) at Weeks 2, 4, 12, 24, and 28
10. Change from Baseline in tissue degradation marker level in urine (desmosine) at Weeks 2, 4, 12, 24, and 28
11. Change from Screening in FVC at Weeks 12 and 24
12. Change from Screening in PEFR at Weeks 12 and 24
13. Change from Screening in FEF_{25-75} at Weeks 12 and 24
14. Total duration (in days) of exacerbations, per subject, over the 24-week treatment period
15. Total number of exacerbations per subject over the 24-week treatment period
16. Time to first pulmonary exacerbation, exacerbation rate, QOL measures, and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by BSI score at Baseline, over the 24-week treatment period
17. Time to first pulmonary exacerbation, exacerbation rate, QOL measures, and pulmonary function parameters (FEV_1, FVC, PEFR, and FEF_{25-75}), stratified by the presence or absence of *Pa* at Screening, over the 24-week treatment period
18. Frequency of use of rescue medications (rescue medications include SABAs, SAMAs, newly prescribed LABAs, LAMAs, and oxygen) over the 24-week treatment period
19. Number of subjects hospitalized due to pulmonary exacerbations by the end of the 24-week treatment period
20. Descriptive assessment of the change in inflammatory and tissue degradation biomarkers and concentration of active NE in blood, sputum, and urine, over the 24-week treatment period

3.2.4. 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. PFT measurements

AESIs that will be reported include hyperkeratosis, periodontitis/gingivitis, and other infections.

3.2.5. Pharmacokinetic Endpoints

The PK parameters, as estimated using non-compartmental analysis methods, will include the following:

1. C_{max}
2. t_{max}
3. Average plasma concentration at steady state (C_{ss})
4. Maximum plasma concentration at steady state ($C_{max,ss}$)t
5. Time to maximum plasma concentration at steady state ($t_{max,ss}$)
6. Minimum plasma concentration at steady state ($C_{min,ss}$)
7. Area under the plasma concentration curve from 0 to 8 hours (AUC_{0-8})

3.3. Discussion of Study Design

3.3.1. Number of Subjects

Approximately 240 subjects with NCFBE 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.

3.3.2. Study Duration

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 EOS (Visit 10), up to 6 weeks for the screening period, 24 weeks for the treatment period and 4 weeks for the follow-up period.

3.3.3. End of Study

The EOS is defined as either the date of the last visit of the last subject to complete the post-dosing follow-up (Visit 10), or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

3.3.4. Stopping Rules

3.3.4.1. Study Discontinuation

For reasonable cause, the Investigator may terminate a subject's participation in the study prematurely; if this occurs, the Investigator must contact the Sponsor immediately. The Sponsor may decide to terminate the study prematurely. If this occurs, written notification of the study termination is required to be sent to all the sites. Some conditions that may warrant study termination include the following:

- Discovery of an unexpected, significant, or unacceptable risk to the subjects in the study

- Decision on the part of the Sponsor to suspend or discontinue development of the investigational product (IP)
- Decision by a regulatory authority or the Sponsor to stop the study at any time, where applicable

If the study is prematurely terminated, all subjects who received a dose of any of the study drugs and have not completed their study period will be discontinued from the study immediately; all the safety procedures (refer to safety procedures during Visit 9) required to be performed will be conducted. All discontinued subjects will be followed up by a phone call 28 days (+/- 3 days) after discontinuation for collection of AEs.

The Sponsor will notify the US Food and Drug Administration (FDA) and any other Regulatory bodies in the respective countries regarding the reason for terminating the study.

3.3.4.2. Subject Discontinuation Criteria

Detailed discontinuation criteria can be found in Section 4.2.1.

3.4. Selection of Doses

3.4.1. Experimental Treatments

This study will have 3 treatment arms of 10 mg, 25 mg, and placebo. The rationale for the dose selection is based on the safety, tolerability, and pharmacodynamic (PD) results (inhibition of NE activity) obtained from the Phase 1 single and multiple dose study of INS1007 in healthy male volunteers' and results of the 6-month toxicity studies in the rats and dogs.

There were no safety findings from the INS1007 Phase 1 single and multiple dose study in healthy male volunteers, where doses up to 65 mg were tested as a single dose and doses up to 40 mg daily were tested as a repeated dose (for 28 days).

In the 6-month dog toxicity study, 2 mg/kg/day was determined to be the NOAEL. The expected safety margin of the 25-mg dose of INS1007 for area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) in plasma was 3.9 (for free INS1007) and 1.7 (for total INS1007), respectively. In the 6-month rat toxicity study, 9 mg/kg/day was determined to be the NOAEL. The expected safety margin of the 25-mg dose of INS1007 for AUC_{0-24} in plasma is 12.4 (for free INS1007) and 26 (for total INS1007).

In the MAD phase of the Phase 1 SAD/MAD study, repeat dosing of 10 mg, 25 mg and 40 mg of INS1007 demonstrated a dose-dependent maximum inhibitory effect on relative normalized NE activity in blood of 39%, 53% and 59%, respectively. In patients with PLS, the loss of DPP1 activity is associated with severe reduction in the activity and stability of neutrophil-derived serine proteases. Neutrophils derived from PLS patients have been described to have less than 10% NSP activity of healthy control neutrophils (Pham et al, 2004). None of the doses assessed for INS1007 reduced NE activity to levels approaching those seen in PLS subjects.

Given the modest increase in inhibitory effect of 40 mg vs. 25 mg, together with the safety margin information resulting from the 6-month dog study, 25 mg was selected as the high dose to be tested in this study. To understand the relationship between the pharmacodynamic effect of INS1007 and clinical outcomes, 10 mg was also selected to be assessed in this study.

The preclinical and clinical PK and PD data obtained to date indicate that INS1007 is an orally bioavailable compound in humans. The data provide adequate steady state exposures at the proposed doses of 10 and 25 mg QD for further evaluation in this Phase 2 study in a subject population with NCFBE. To ensure target engagement and to allow enough time for the inhibitory effects of the NSPs' activities to be translated into bronchial beneficial effects via decreasing bronchial inflammation and mucus hypersecretion, a dosing period of 24 weeks is chosen, which is supported by the currently available 6-month animal toxicity studies in rats and dogs.

3.4.2. Control Treatments

This study is planned to have 1 placebo control arm. The dosage form will be identical in appearance to the experimental drugs but with no active ingredient.

3.5. Data Monitoring Committee

An independent, external Data Monitoring Committee (DMC), comprising at least 2 physicians with pulmonary expertise, an expert in periodontal disease, an expert in dermatology, and a statistician who is experienced in the evaluation of clinical safety data will be set up to review all AEs and SAEs to ensure the safety of subjects enrolled into this study. Additional members may be added by the DMC if it is determined that additional expertise is required to evaluate the clinical safety data. The DMC members will review the data in a semi-blinded or un-blinded manner at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review those data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. Further details of the DMC will be provided separately in the DMC charter.

4. STUDY POPULATION

4.1. Enrollment

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

4.1.1. Inclusion Criteria

Subjects eligible for enrollment in the study must meet all the following criteria:

1. Give their signed study informed consent to participate
2. Are male or female between 18 and 85 years of age (inclusive) at Screening
3. Have a BMI > 18.5 at Screening
4. Have a clinical history consistent with NCFBE (cough, chronic sputum production and/or recurrent respiratory infections) that is confirmed by chest CT demonstrating bronchiectasis affecting 1 or more lobes (confirmation may be based on prior chest CT). Subjects whose past chest radiographic image records are not available will undergo a chest CT scan during Screening.
5. Are current sputum producers with a history of chronic expectoration, and able to provide sputum sample during Screening. If a subject is unable to produce sputum spontaneously during Screening (Visit 1), the subject will be considered a screen failure. The subject may not undergo a sputum induction procedure during Screening (Visit 1) to meet inclusion criterion.
6. Have a sputum color at Screening of mucoid purulent or purulent as assessed by the sputum color chart (Murray et al, 2009)
7. Have at least 2 documented pulmonary exacerbations defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before Screening
8. Women must be post-menopausal (defined as no menses for 12 months without an alternative medical cause), surgically sterile, or using highly effective contraception methods (ie, methods that alone or in combination achieve < 1% unintended pregnancy rates per year) from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner. All WOCBP must have a negative pregnancy test before randomization.

   Note: Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual lifestyle of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides

only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

9. Males with female partners of childbearing potential must be using effective contraception from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study), combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone-releasing systems, or vasectomized partner. Note: Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual lifestyle of a subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception.

   Note: Male subjects will be advised of the potential toxicity to sperm observed in nonclinical studies and will be advised not to participate in the study if they plan to father a child in the future.

4.1.2. Exclusion Criteria

Subjects meeting any of the following criteria are to be excluded:

1. Have a primary diagnosis of COPD or asthma as judged by the Investigator
2. Have bronchiectasis due to CF, hypogammaglobulinemia, common variable immunodeficiency, or α1-antitrypsin deficiency
3. Are current smokers as defined per Centers for Disease Control and Prevention (CDC) criteria detailed in the protocol (Section 7.5.2)
4. Are currently being treated for a nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis
5. Have any acute infections (including respiratory infections) that required antibiotic treatment within 4 weeks before Screening or within 12 weeks before Screening if the antibiotic prescription is a macrolide
   a. If a subject suffers an exacerbation or infection requiring antibiotic treatment after the Screening visit, but prior to randomization, the subject will be considered a screen failure.
6. Are unable to perform technically acceptable spirometry meeting American Thoracic Society (ATS)/European Thoracic Society (ERS) acceptability criteria with at least 3 acceptable flow-volume curves with at least 2 meeting the ATS/ERS repeatability criteria for FEV_1 during Screening
   a. Subjects who need to repeat PFTs because they do not meet the exclusion criterion can repeat the test up to 2 times without being re-screened.
7. Have an abnormal renal function test result (estimated glomerular filtration rate [eGFR] < 45 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) at Screening

8. Have elevated liver function test results (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 2 × upper limit of normal [ULN]) at Screening
9. Have a bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening
10. Have a current or chronic history of liver disease (Child-Pugh A, B, or C), or known hepatic or biliary abnormalities except for Gilbert's syndrome or asymptomatic gallstones, and/or positive serological tests for hepatitis B, hepatitis C (HCV), or known human immunodeficiency virus (HIV) infection
11. Have a white blood cell count < lower limit of normal at Screening
12. Have any clinically significant abnormal laboratory values at Screening or diseases or disorders (eg, cardiovascular, pulmonary, gastrointestinal, liver, kidney, neurological, musculoskeletal, endocrine, metabolic, psychiatric, physical impairment, or a lung transplantation) that, in the opinion of the Investigator, may put the subject at risk by participating in the study, or interfere with the subject's treatment, assessment, or influence the results of the study, or have compliance issues with the study
13. Are taking cyclic doses of antibiotics as chronic treatment for NCFBE
14. Are taking oral or inhaled antibiotics as chronic treatment for NCFBE < 6 months prior to Baseline, patients on antibiotics as chronic treatment should be on such treatment for at least 6 months prior to enrolment while meeting all other inclusion and exclusion criteria
15. Are taking concomitant medications that may cause hyperkeratosis (eg, tumor necrosis factor [TNF-α] antagonists)
16. Are not on a stable dose of an inhaled corticosteroid for at least 4 weeks prior to Day 1 if the subject is currently on an inhaled corticosteroid
17. Are unable to withhold SABA or SAMA use for at least 6 hours prior to PFTs or unable to withhold LABA or LAMA use on the day PFTs will be performed until after the test
18. Have a history of malignancy in the past 5 years with exception of non-melanoma skin cancer
19. Have a baseline-corrected QT interval by Fridericia (QTcF) > 450 milliseconds (males) or 470 milliseconds (females) or history of congenital long QT syndrome, or Torsades de Pointes or other abnormal ECG at Screening or Baseline (unless the ECG findings are not clinically significant and are approved by the Investigator and documented by signature)
    a. If a subject does not qualify due to ECGs that do not meet the quality criteria, the subject can repeat the test up to 2 times without being re-screened.
20. Have significant hemoptysis (≥ 300 mL or requiring blood transfusion) within 6 weeks prior to Day 1 (Visit 2)
21. Are currently participating in or scheduled to participate in an intensive pulmonary rehabilitation program (a maintenance rehabilitation program is allowed if their schedule and procedure will be kept consistent during the duration of the study)

22. Participated in any other interventional clinical studies within 3 months before Day 1 (Visit 2)

Have the following medical conditions associated with the onset of non-hereditary palmoplantar keratosis:

23. Hypothyroidism, myxedema, chronic lymphedema, acrocyanosis, or livedo reticularis

    Note: If a subject has hypothyroidism but is currently being treated, and thyroid-stimulating hormone (TSH) and/or triiodothyronine (T3)/thyroxine (T4) are within normal ranges, the subject is allowed into the trial.

24. Have psoriasis or lichen planus
25. Have Reiter's disease/keratoderma, or blennorrhagicum, or "reactive arthritis"
26. Have pityriasis rubra pilaris, or atopic dermatitis, or chronic hand dermatitis, or chronic contact dermatitis, or chronic dermatophytosis
27. Have chloracne, or extensive verruca vulgaris, or keratoderma climactericum
28. Perform extreme running or swimming, or other chronic, repetitive mechanical or water damage to plantar epidermis

Periodontal disease (to be evaluated by a periodontist or dentist):

29. Have any tooth that can potentially cause pain or infection as noted in the oral exam unless they are corrected before the study
30. Have severe periodontal disease as defined as with pocket depth measurements and attachment loss $\geq$ 6 mm on 2 or more teeth
31. Have Class-3 mobility or 3 furcation involvement
32. Are scheduled to have tooth extraction that will occur during the study period

Papillon-Lefèvre Syndrome:

33. Have a clinical diagnosis of PLS

4.2. Removal of Subjects

4.2.1. Reasons for Withdrawal/Early Discontinuation

A subject may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator. When this occurs, the subject should complete all the procedures at the Visit 9 (End of Treatment) Visit. Subjects who discontinue the treatment due to AEs should remain under observation until the resolution or stabilization of the AEs.

A subject may be discontinued from the study drug treatment before completion for any of the following reasons:

1. Subject death
2. Subject experiences an AE(s)/SAEs that warrants discontinuation, as judged by the Investigator and/or Insmed

3. A major protocol deviation, which, in the opinion/discretion of the Investigator and/or Insmed compromises the data integrity of the study
4. Subject is noncompliant with the study drug treatment
5. Treatment code is prematurely broken by the Investigator
6. Subject withdraws consent
7. Subject decision to discontinue treatment
8. Sponsor terminates the study
9. Investigator discretion
10. Subject lost to follow-up
11. Subject pregnancy
12. Periodontal criteria met
13. Skin criteria met
14. Serious infection, defined as life-threatening infections, infections requiring hospitalization, or infections requiring treatment with intravenous antibiotics (except hospitalizations for exacerbations, where the PI will evaluate whether it is in the best interest of the subject to continue in the study)
15. Subjects who develop neutropenia defined as ANC < $1000/mm^3$

Except for those subjects who withdraw consent, die or are lost to follow-up, subjects who discontinue their assigned study drug will be encouraged to continue to participate in their remaining scheduled study visits. Every effort should be made by the Investigator to keep these subjects in the study through Visit 10. "Lost to follow-up" should be marked only in an exceptional case when all documented attempts to reach the subject by the Investigator or other staff members were unsuccessful.

4.2.2. Subject Re-Screening Procedures

Subjects who do not meet eligibility criteria during Screening may be re-screened up to 2 times if approved by Insmed's Medical Monitor.

During Screening (Visit 1), if a subject does not qualify due to ECGs that do not meet the quality criteria, the subject can repeat the test up to 2 times without being re-screened.

Subjects who need to repeat PFTs because they do not meet exclusion criterion 6 (Section 4.1.2) can repeat the test up to 2 times without being re-screened.

Subjects who are considered a screen failure for reasons not related to the dental exclusion criteria (Section 4.1.2, 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.

5. STUDY TREATMENTS

5.1. Investigational Products

5.1.1. Investigational Product

INS1007 is a film-coated, oral tablet available in dose strengths of 10 mg and 25 mg. The 2 strengths are round, biconvex, brown film-coated tablets identical in size and appearance. The tablets are an immediate-release dosage form with rapid dissolution characteristics under *in vitro* test conditions.

Each tablet contains active ingredient INS1007 and the following inactive US Pharmacopeia/National Formulary or European Pharmacopoeia compendia ingredients: microcrystalline cellulose, dibasic calcium phosphate dihydrate, sodium starch glycolate, silicon dioxide, and glyceryl behenate. The tablet is film coated with hypromellose, polyethylene glycol, titanium dioxide, iron oxide red, iron oxide yellow, and iron oxide black.

5.1.2. Matching Placebo

The matching placebo tablet contains microcrystalline cellulose and sodium stearyl fumarate and is coated identically to INS1007 tablets.

5.1.3. Method of Assigning Subjects to Treatments and Blinding

Subjects will be randomized in a blinded fashion via an RTSM system into 1 of 3 treatment arms to receive either 10 mg or 25 mg of INS1007 or matching placebo in a 1:1:1 ratio.

5.1.4. Unblinding Procedures

In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study treatment is not sufficient, and the study treatment must be unblinded to evaluate further course of action, the Investigator can unblind study treatment for a specific patient. It is suggested that the Investigator contact the Insmed Medical Monitor or appropriate Insmed study personnel prior to the unblinding. The Investigator must be able to confirm that unblinding of the subject is necessary and directly impacts the subject's immediate medical management or welfare of the subject. The subject will be considered discontinued from the study.

If this is not possible, the Investigator must notify the Sponsor as soon as possible. The date and reason for unblinding must be documented and signed by the study Investigator. The originally signed copy is maintained in the study file at the site, and a copy is provided to the Sponsor or its designee. The Investigator should follow the steps in the Medidata Balance RTMS system and enter the unblinding date and reason. The date and reason for the unblinding is also entered in the study eCRF and any associated AE reports.

5.1.5. Study Drug Administration

INS1007 is administered orally, QD before breakfast and should be taken with a glass of water on an empty stomach at approximately the same time every day. Tablets should not be broken or chewed. If a dose is forgotten but remembered before midnight of that day, the missed dose should be taken immediately. Otherwise, the dose should be skipped for that day.

5.1.6. Method of Assessing Treatment Compliance

Subjects will be advised to bring all their unused study drug along with their handheld computer tablet to each visit during the treatment period. Site staff are responsible to review the dosing diary and reconcile with the untaken study drug. Drug accountability will be recorded into the source documents and eCRF at each study visit.

Accountability for study drug administration during the study is the responsibility of the Investigators or designees. The Investigators will document the number of tablets dispensed to and returned by each subject at each visit after reviewing their dosing diary. Compliance will be defined as taking between 80% and 125% of the intended quantity of the study drugs.

5.1.7. Packaging and Labeling Information

Labels will be prepared in accordance with Good Manufacturing Practice Annex 13 requirements and local regulatory guidelines. Label text will be translated into local language. The study drug label on the bottle specifies the appropriate storage.

INS1007 and matching placebo will be packed in individual high-density polyethylene bottles, labeled and stored as described below.

Number	Label Requirements	Specific Label Information
1	Pharmaceutical dosage form	Oval, biconvex, brown, film coated tablet
2	Quantity of the dosage unit	10 mg, 25 mg, or placebo
3	Protocol number	INS1007-201
6	Lot number	Subject specified
7	Re-Test/Expiration date	As provided
8	Caution statement	For clinical study use only.
9	Storage conditions	At room temperature, below 30°C
10	Sponsor identification, name, address and phone number	Insmed Incorporated 10 Finderne Avenue Bridgewater, NJ 08807 [redacted]
11	Direction for use	This product should only be used after appropriate training.
12	Statement: *"Keep out of sight and reach of children"*	Keep out of sight and reach of children.

5.1.8. Storage

All study drug supplies must be stored in accordance with the label information. Until dispensed to the study subjects, the study drugs will be stored at room temperature between 2°C and 30°C, at the sites in a securely locked, limited access storage area under appropriate storage conditions, accessible to authorized personnel only.

5.1.9. Drug Usage and Accountability

The study drugs are to be prescribed only by the Investigators or sub Investigators participating in the trial.

Under no circumstances will the Investigators allow the study drugs to be used other than as directed by this protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and maintain accurate records accounting for the receipt of the study drug supplies and for the disposition of the study drugs on an ongoing basis. In addition, the Investigator or designee shall contact Insmed as soon as possible if there is a problem with the shipment.

Documentation of the disposition of the study drugs should consist of a Site Study Drug Accountability Log and a Subject Study Drug Accountability Log.

- The study drugs dispensed to the site will be recorded in the Site Study Drug Accountability Log (or equivalent document approved by the Sponsor).
- The study drugs dispensed to each subject will be recorded in the Subject Study Drug Accountability Log (or equivalent document approved by the Sponsor).

The Site Study Drug Accountability Log should include identification of all subjects by their subject numbers to whom the study drugs are dispensed, the total quantity and date of dispensing, and the total quantity of used and unused study drugs.

The Subject Study Drug Accountability Log should include identification of subject by their subject number to whom the drug is dispensed, the quantity and the date of dispensing, and the quantity of used study drugs. This record is in addition to any drug accountability information recorded on the eCRFs.

The Site and Subject Study Drug Accountability Logs will be verified by the Sponsor's study monitor or its designee at each monitoring visit.

Upon completion of the study, the Investigators must return all the unused study drugs and all partially dispensed or empty bottles to the Sponsor or its designee, or dispose of them locally per applicable local and country regulations. Any used and unused study drugs will be maintained by the sites until inventoried by the Sponsor study monitors or designees before return or disposal locally. Drug supply destruction must be clearly documented and kept in the study file at sites, and a copy should be provided to the Sponsor or its designee. The Investigators shall also provide a written explanation for any missing study drugs if it occurs with the original kept in the study file at the sites and a copy to the Sponsor.

The original Site and Subject Study Drug Accountability Logs will be approved and signed by the Investigators and retained at the study sites and a copy supplied to the Sponsor or its designee after the study is completed.

5.2. Concomitant Medications

Any medications the subject takes other than the study drugs from Visit 2 (Baseline, Day 1) to Visit 10 (EOS, Day 197) are considered concomitant medications and will be collected and documented in the study eCRF.

Any procedures performed from Visit 2 (Baseline, Day 1) to Visit 10 (EOS, Day 197) are considered concomitant procedures and will be collected and documented in the study eCRF.

5.3. Prohibited Medications

Use of any immunomodulatory agents (eg, bortezomib, ixazomib, and thalidomide) is prohibited during the study through Visit 10 (EOS).

Continuous use of high dose non-steroidal anti-inflammatory drugs is prohibited during the study through Visit 10 (EOS) unless the use is considered necessary per Investigator discretion.

Medications that may cause a palmoplantar keratoderma are prohibited during the study through Visit 10 (EOS). Please refer to Table 1 for the list of medications that may cause palmoplantar keratoderma.

Table 1: Prohibited Medications (May Cause Palmoplantar Keratoderma)

Common Generic Name	Required Washout Period
Arsenic Fowler's Solution for Psoriasis Dioxin Glucan Tegafur/Fluorouracil Bleomycin Hydroxyurea Lithium Venlafaxine Quinacrine Imatinib Mesylate	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up

The drug-drug interaction clinical study results, Study D6190C00003, indicate that there was little or no effect of a strong CYP3A4/5 inhibitor (itraconazole) on the exposures of INS1007. Drugs that inhibit CYP isoforms will be permitted during this study; however, co-administration of inhibitors of more than one INS1007 elimination pathway (eg, CYP3A4/5 with CYP2C8 and/or CYP2D6 inhibitors) should be avoided, as there is no information on their combined drug-drug interaction potential (refer to Table 2 and Table 3 for a representative list of known CYP2C8 and CYP2D6 inhibitors, and a list of CYP3A4 inhibitors).

As no clinical data exists on the effect of inducers of CYP3A4/5 on the PK of INS1007, moderate and strong inducers will not be allowed during the study (refer to Table 4 for common CYP3A4/5 inducers).

Table 2: List of Moderate and Strong CYP2D6 and CYP2C8 Inhibitors (not to be Co-Administered With CYP3A4/5 Inhibitors but Otherwise Permitted)

Common Generic Name	Required Washout Period
Moderate CYP2C8 Inhibitors	
Deferasirox Teriflunomide Trimethoprim	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up
Strong CYP2C8 Inhibitors	
Clopidogrel Gemfibrozil	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up
Moderate CYP2D6 Inhibitors	
Cinacalcet Duloxetine Sertraline Terbinafine	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up
Strong CYP2D6 Inhibitors	
Bupropion Fluoxetine Paroxetine Quinidine	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up

CYP = cytochrome P450 enzyme.

Table 3: List of Moderate and Strong CYP3A4/5 Inhibitors (Permitted Unless Combined With the Above Moderate and Strong CYP2D6 and CYP3C8 Inhibitors)

Common Generic Name	Required Washout Period
Moderate CYP3A4/5 Inhibitors	
Aprepitant Atazanavir Atazanavir/Ritonavir Fluconazole Verapamil Diltiazem Amprenavir Atazanavir Ciprofloxacin Darunavir/Ritonavir Fosamprenavir Imatinib Cimetidine Cyclosporine Fluvoxamine Posaconazole	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up
Strong CYP3A4/5 Inhibitors	
Boceprevir Telaprevir Lopinavir/Ritonavir Saquinavir Indinavir Mibefradil[a] Nelfinavir Clarithromycin Telithromycin Conivaptan Itraconazole Ketoconazole Posaconazole Nefazodone Voriconazole Grapefruit Juice (Also Pomelo, Grapefruit, Seville Oranges, Seville Orange Marmalade, or Other Products Containing Grapefruit or Seville Oranges)[b]	4 weeks prior to Day1 to 28-day (+/- 3 days) Safety Follow-Up

CYP = cytochrome P450 enzyme

[a] Withdrawn from various markets such as the United States because of safety reasons.

[b] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation- dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

Table 4: Prohibited Medications (CYP3A4/5 Inducers)

Common Generic Name	Required Washout Period
Moderate CYP3A4/5 Inducers	
Bosentan Efavirenz Etravirine Modafinil Nafcillin	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up
Strong CYP3A4/5 Inducers	
Avasimibe[a] Phenobarbital Carbamazepine Phenytoin Rifampin Rifabutin St. John's Wort[b] Troglitazone	4 Weeks Prior to Day1 to 28-Day (+/- 3 Days) Safety Follow-Up

[a] Not a marketed drug.
[b] The effect of St John's Wort varies widely and is preparation-dependent.
CYP = cytochrome P450 enzyme.

As a rule, no companion medication that has been tolerated and is considered necessary by the Investigator for the treatment of the subjects' underlying disease or comorbidities shall be withheld in any subject to fulfill eligibility for this study.

If the use of any prohibited medications is necessary, they may be allowed upon consultation with the Sponsor and should be taken cautiously under close monitoring.

5.4. Permitted Medications and Procedures

Any concurrent ongoing medications, including over-the-counter drugs are allowed if not prohibited by the protocol (see Section 5.3).

Subjects should continue their maintenance doses of oral or inhaled antibiotics or inhaled corticosteroids during the study. Subjects can use LABA, LAMA, anticholinergic bronchodilators, PDE4 inhibitors, and their reliever medication (SABA, SAMA) during the study if prescribed by their physicians. Subjects are also allowed to continue their airway clearance maintenance treatment/procedures such as use of hypertonic saline/isotonic saline, mucolytics, and pulmonary rehabilitation. However, except under unforeseeable clinical circumstances, the airway clearance maintenance treatment/procedures and pulmonary rehabilitation should continue unchanged throughout the duration of the study through Visit 10 (EOS).

The use of selective serotonin receptor inhibitors (SSRIs) is allowed if the subject has been receiving them for at least 6 months prior to the study. Subjects are not allowed to start SSRIs during the study.

There is a minimum time interval restriction for some of the medication use before and after spirometry testing. The minimum time intervals of the restricted medications are summarized in Table 5.

Table 5: Minimum Time Intervals for Restricted Medication Use Prior to Reversibility/Spirometry Testing

Medication	Minimal Time Interval From Last Medication Dose Prior to Post-Bronchodilator Testing
Inhaled SABA (Salbutamol/Albuterol, Terbutaline)	6 Hours
Inhaled LABA, Including ICS/LABA Combination Products	
Formoterol	12 Hours
Salmeterol	12 Hours
Olodaterol	24 Hours
Indacaterol	24 Hours
Oral β_2-Agonists: Short-Acting Long-Acting	6 Hours 24 Hours
Transdermal β_2-Agonists	24 Hours
Inhaled SAMA (Ipratropium)	6 Hours
Inhaled LAMA, Including LAMA/LABA and ICS/LAMA Combination Products	
Aclidinium	12 Hours
Tiotropium	24 Hours
Glycopyrrolate	24 Hours
Umeclidinium	24 Hours
Xanthines	
Twice Daily	12 Hours
Once Daily	24 Hours
Roflumilast	24 Hours
Ephedrine-Containing Drugs	6 Hours
Leukotriene Receptor Antagonists	Allowed

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; NA = not applicable; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist.

6. STUDY PROCEDURES

A Study Schedule of Events is provided in Table 6.

6.1. Screening Period

The screening period is from Day -42to Day -1. During this screening period, the procedures and assessments required at Visit 1 will be performed.

6.1.1. Visit 1 (Days -42 to -1)

The following procedures and assessments will be performed during Screening.

- Informed consent
- Review of eligibility criteria
- Demographic information
- Height, weight and BMI calculation
- Smoking history
- Relevant medical history review
- Physical examination
- Vital signs (BP, HR, T, and respiration rate [RR])
- 12-lead ECG
- PFT by spirometry
- Chest CT Scan (to be performed only if the subject does not have prior radiological confirmation of bronchiectasis diagnosis)
- Clinical laboratory tests (hematology, blood chemistry and urinalysis)
- Special laboratory tests (ie, C-reactive protein, prothrombin time)
- Hepatitis B surface antigen (HBsAg), HIV, and HepC Ab
- Serum pregnancy test for WOCBP
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers.
- Sputum microbiology culture and review for *Pa*
- eGFR calculation
- Dental examination
- Review and documentation of prior and concomitant medications
- Review and documentation of AEs
- Child–Pugh Score (only for subjects whose liver function tests are abnormal and suspected to have chronic liver disease to assess for eligibility)

6.2. Treatment Period Visits 2 Through 9

6.2.1. Visit 2 (Baseline, Day 1) Randomization

The following procedures and assessments will be performed during Visit 2.

- Confirm eligibility prior to randomization
- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- 12-lead ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Review and confirmation of eligibility criteria
- Randomization by Medidata Balance RTSM system
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Blood and urine sample collection for evaluating NE and other biomarkers
- Study drug dispensing and review of dosing diary
- SGRQ
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Medical Research Council Breathlessness Scale assessment and BSI Calculation
- Dental hygiene education
- PK sampling (see Table 6 footnote J for sampling details)
- Sputum induction procedure to collect sputum sample, if needed

6.2.2. Visit 3 (Week 2, Day 15)

The following procedures and assessments will be performed during Visit 3.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status

- Vital signs (BP, HR, T, and RR)
- 12-lead ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein and prothrombin time)
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Blood and urine sample collection for evaluating NE and other biomarkers
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Review of dosing diary
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions
- PK sampling (see Table 6 footnote J for sampling details)
- Sputum induction procedure to collect sputum sample, if needed

6.2.3. Visit 4 (Week 4, Day 29)

The following procedures and assessments will be performed during Visit 4.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- 12-lead ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Blood and urine sample collection for evaluating NE and other biomarkers
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed

- Study drug dispensing and review of dosing diary
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions
- PK sampling (see Table 6 footnote J for sampling details)
- Sputum induction procedure to collect sputum sample, if needed

6.2.4. Visit 5 (Week 8, Day 57)

The following procedures and assessments will be performed during Visit 5.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- 12-lead ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Dental examination (can be performed ± 7 days of visit date)
- Study drug dispensing and review of dosing diary
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions.

6.2.5. Visit 6 (Week 12, Day 85)

The following procedures and assessments will be performed during Visit 6.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications

- Smoking status
- Physical examination
- Vital signs (BP, HR, T, and RR)
- PFT by spirometry
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Blood and urine sample collection for evaluating NE and other biomarkers
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Study drug dispensing and review of dosing diary
- SGRQ
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions
- PK sampling (see Table 6 footnote J for sampling details)
- Sputum induction procedure to collect sputum sample, if needed

6.2.6. Visit 7 (Week 16, Day 113)

The following procedures and assessments will be performed during Visit 7.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- 12-lead ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP

- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Study drug dispensing and review of dosing diary
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions

6.2.7. Visit 8 (Week 20, Day 141)

The following procedures and assessments will be performed during Visit 8.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Study drug dispensing and review of dosing diary
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- Dental hygiene education
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions

6.2.8. Visit 9 (Week 24, Day 169, End of Treatment)

The following procedures and assessments will be performed during Visit 9.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Physical examination

- Vital signs (BP, HR, T, and RR)
- Weight
- 12-lead ECG
- PFT by spirometry
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)
- Urine pregnancy test for WOCBP
- Blood and urine sample collection for evaluating NE and other biomarkers
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Sputum microbiology culture and review for *Pa*
- eGFR calculation
- Dental examination (can be performed ± 7 days of visit date)
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions
- Review of dosing diary
- SGRQ
- QOL-B
- LCQ
- Pulmonary exacerbation symptom entry and review
- PK sampling (see Table 6 footnote J for sampling details)
- Sputum induction procedure to collect sputum sample, if needed

6.2.9. Visit 10 (Week 28, Day 197, End of Study)

The following procedures and assessments will be performed during Visit 10.

- Review and documentation of AEs
- Review and documentation of prior and concomitant medications
- Smoking status
- Vital signs (BP, HR, T, and RR)
- Physical examination
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Special laboratory tests (C-reactive protein, prothrombin time)

- Urine pregnancy test for WOCBP
- Blood and urine sample collection for evaluating NE and other biomarkers
- Collection of urine sample for urine protein and creatinine quantitative test to assess renal function, if needed
- Sputum sample collection for sputum color determination and evaluating NE and other biomarkers
- Pulmonary exacerbation symptom entry and review
- Assessment of oral infection, gingivitis, periodontitis, and skin conditions
- PK sampling (see Table 6 footnote J for sampling details)

6.2.10. Unscheduled Study Visits

Subjects will be advised to contact their study site should they feel their respiratory symptoms are worsening or if they experience an AE that they may consider related to the study drug. The Investigator will then decide whether the subject should have an unscheduled study visit to further assess their respiratory symptoms for a potential pulmonary exacerbation or any AE related to the study drug. During the unscheduled visit, it is recommended that vital signs and safety laboratory tests will be performed; AEs and concomitant medications will be reviewed; a sputum sample will be collected for measuring NE concentration. Subjects will be reminded to contact the site if symptoms worsen and if they suspect they may be suffering a pulmonary exacerbation. If possible, subjects will be asked to visit the site for an unscheduled visit. If not possible, the Investigator should evaluate subject's symptoms by phone.

Table 6: Schedule of Events

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -42 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) [c]	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	
Clinical Laboratory Tests (Hematology, Blood Chemistry and Urinalysis)[b, c]	X	X[c]	X	X	X	X	X	X	X	X

Procedure	Screening Period	Treatment Period								End of Study Visit
	Days -42 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)
Special Laboratory Tests (C-Reactive Protein and Prothrombin Time)	X	X	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 -42 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 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 -42 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
Urine Protein and Creatinine Quantitative Test and Ratio Calculation[m]			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)**	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 (Section 4.1.1, inclusion criterion 5). 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 but none of the 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 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.
Subjects who are considered a screen failure for reasons not related to the dental exclusion criteria (Section 4.1.2, 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.

[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, and 9. Collection of PK sample at visit 10 will be done anytime either pre- or post-dose during the visit. For subjects who participate in the PK sub-study, the Visit 4 window will be ± 5 days.
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).
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.

[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; CT = computed 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.

7. STUDY VARIABLES AND METHODS OF ASSESSMENTS

7.1. Primary Endpoint Variable

7.1.1. Time to First Pulmonary Exacerbation

Pulmonary exacerbation symptoms will be collected and reviewed throughout the study at Visits 2 through 10 (refer to Table 6). The time to first pulmonary exacerbation over the 24-week treatment period (Visits 2 through 9) will be analyzed.

A pulmonary exacerbation in this study is defined as having three 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 criteria of exacerbation.

7.2. Secondary Endpoint Variables

7.2.1. Quality of Life Questionnaire-Bronchiectasis

The 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, 2015; Quittner et al, 2014). 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 QOL-B will be provided to the study subjects in an electronic format on a hand-held computer tablet after randomization. Subjects will be required to complete the QOL-B after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).

The subjects will complete the questionnaire while they are in the clinic at each of the study visits and at home for the weeks in between the study visits. It is important for the site staff to remind the subjects to bring their computer tablets with them to each clinic visit.

The completed questionnaires will be reviewed during each visit. Subjects will be re-trained on how to complete the questionnaires correctly, if needed. The Respiratory Symptoms Domain score of the QOL-B will be assessed as a secondary endpoint. The other domain scores of the QOL-B will be assessed as exploratory endpoints.

A hard copy of the QOL-B and the "Instructions for Completing the QOL-B" will be provided separately.

7.2.2. Pulmonary Function Test

Post-bronchodilator pulmonary function test by spirometry (FEV_1, FVC, PEFR, and FEF_{25-75}) will be performed per the ATS/ERS criteria (Miller et al, 2005) at Visit 1 (Screening), Visit 6, and Visit 9 (refer to Table 6). Subjects should be provided with the detailed instruction on how to conduct the FVC maneuver per ATS/ERS spirometry standardization before performing the test. Forced expiratory volume in 1 second will be assessed as a secondary endpoint. The other parameters of the PFT will be assessed as exploratory endpoints.

Subjects should be advised to withhold short-acting inhaled drugs (eg, the β-agonist albuterol/salbutamol or the anticholinergic agent ipratropium bromide) within 6 hours prior to the test. Long-acting β-agonist bronchodilators (eg, salmeterol or formoterol) or long-acting muscarinic bronchodilators (eg, tiotropium) or oral therapy with aminophylline or slow release β-agonists should be withheld for 12-24 hours depending on the medication used (refer to Table 5) for the minimum time intervals for a list of restricted medications) prior to the testing.

Subjects should be advised to withhold the use of their inhaled corticosteroids at least 24 hours prior to the test. In the event a subject has taken a restricted medication during the specified time interval before the test, the test should be rescheduled for another visit within the protocol-specified visit window. If rescheduling the visit is not feasible for the subject, the test should be conducted as usual with appropriate notation in the source documents.

Subjects should be advised to rest at least 30 minutes, and not to eat a large meal for at least 2 hours prior to the test. If a subject is scheduled to have pulmonary rehabilitation on the day of their visit, they should be advised to have the PFT done before the rehabilitation on that day.

Post-bronchodilator spirometry tests will be performed per the following instructions:

When an inhaled SABA is used, 4 puffs of albuterol, levalbuterol, or terbutaline will be administered. A post-bronchodilator PFT will be performed 15 to 30 minutes after the administration of albuterol or levalbuterol. If another SABA is used, Insmed should be contacted for further directions.

When an inhaled SAMA is used, 4 puffs of ipratropium will be administered. A post-bronchodilator PFT will be performed 30 minutes after the administration of ipratropium.

If a patient cannot perform an inhalation, the SABA or SAMA can be nebulized. Pulmonary function tests should be performed 30 minutes after finalization of nebulization

If a patient used SABA in the first assessment of PFTs, the same SABA and mode of administration should be used in subsequent assessments. If a patient used SAMA in the first assessment of PFTs, the SAMA and mode of administration should be used in subsequent assessments.

Detailed instruction on how to conduct the spirometry and document the results are provided in a separate spirometry manual.

7.2.3. Neutrophil Elastase Concentration - Sputum

Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6).

If a subject is unable to produce sputum spontaneously during any visit, the subject should undergo a sputum induction procedure. The detailed sputum induction procedure is described in Appendix 1.

The detailed instruction on the sputum sample collection, processing and shipment will be provided in a separate laboratory manual.

7.2.4. Rate of Pulmonary Exacerbation

Pulmonary exacerbation (defined by symptoms, duration of symptoms and antibiotic prescription) will be collected and reviewed throughout the study at Visits 2 through 10 (refer to Table 6). The rate of pulmonary exacerbations (number of events per person-time) over the 24-week treatment period will be analyzed and the analysis population stratified by *Pa* colonization status and maintenance macrolide antibiotic use at Baseline.

Pulmonary exacerbations are defined in Section 7.1.1.

7.3. Exploratory Endpoint Variables

7.3.1. Leicester Cough Questionnaire

The LCQ is a validated PRO questionnaire evaluating cough on QOL 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 7-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 LCQ will be provided to the study subjects in an electronic format on a handheld computer tablet after Randomization. Subjects will be required to complete the LCQ after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet every 2 weeks from Visits 2 through 9 (refer to Table 6).

The subjects will complete the questionnaire while they are in the clinic at each of the study visits and at home for the weeks in between the study visits. It is important for the site staff to remind the subjects to bring their computer tablets with them to each clinic visit.

The completed questionnaires will be reviewed during each visit. Subjects will be re-trained on how to complete the questionnaires correctly, if needed.

7.3.2. St. George's Respiratory Questionnaire

The SGRQ is a self-administered PRO with 50 questions designed to measure and quantify health-related health status in subjects with chronic airflow limitation (Jones et al, 1991). The SGRQ assesses health related QOL by evaluating 3 health domains: Symptoms (distress caused

by respiratory symptoms), activity (effects of disturbances to mobility and physical activity), and impact (the effect of disease on factors such as employment, personal control of one's health, and need for medication). It has been shown to correlate well with the established measures of the 3 domains in subjects with asthma and COPD. It has also been validated for use in NCFBE.

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

The SGRQ will be provided to the study subjects in an electronic format on a handheld computer tablet after randomization. Subjects will be required to complete the SGRQ after the training and prior to the administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will complete the questionnaire directly on the computer tablet at Baseline (Visit 2), Week 12 (Visit 6) and Week 24 (Visit 9). It is important for the site staff to remind the subjects to bring their computer tablets with them to each clinic visit.

The completed questionnaires will be reviewed during each visit. Answers to some possible questions are provided in the "Guide to Completing the SGRQ" section following the questionnaire. The study coordinator should review these guidelines before seeing subjects to prepare for their questions.

7.3.3. Neutrophil Elastase Concentration – Blood

Blood samples will be collected at Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6).

Detailed instruction for the blood sample collection, processing and shipment will be provided in the site study binder.

7.3.4. Sputum Color

Sputum color will be evaluated by the Investigator (must be an MD) against the sputum chart developed by Murray (Murray et al, 2009). Where possible, the same Investigator should perform the sputum color determination at each evaluation for a subject. The actual chart will be provided in the site study binder. The color on the chart corresponding to the closest color of the sputum will be recorded in the study source document and eCRF.

Sputum samples will be collected from subjects at Visit 1 (Screening), Visit 2 (Baseline), Visits 3, 4, 6, 9, and 10 (refer to Table 6).

7.3.5. Inflammatory Biomarker Levels-Sputum

Sputum samples will be collected at Screening (Visit 1), Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of NE concentrations (refer to Table 6:). Only NE, proteinase 3, and cathepsin G will be analyzed.

If a subject is unable to produce sputum spontaneously during any visit, the subject should undergo a sputum induction procedure (a subject may not undergo a sputum induction procedure during Screening [Visit 1] to meet eligibility [Section 4.1.1, inclusion criterion 5]). The detailed sputum induction procedure is described in Appendix 1.

Detailed instructions on the sputum sample collection, process and shipment will be provided in the site study binder

7.3.6. Inflammatory and Tissue Degradation Biomarker Levels - Blood and Urine

Blood and urine samples will be collected at Baseline (Visit 2), and Visits 3, 4, 6, 9, and 10 for measurement of inflammatory and tissue degradation biomarkers (refer to Table 6).

Note: Samples will only be collected at sites with PK sample processing capabilities.

The detailed instruction for the blood sample collection, processing and shipment will be provided in the site study binder.

7.3.7. Exacerbation Duration

Pulmonary exacerbation symptoms will be collected and reviewed by the Investigator (must be an MD) throughout the study at Visits 2 through 10 (refer to Table 6). Exacerbations will be defined as described in Section 7.1.1. The total duration, in days, of exacerbations, per subject, over the 24-week treatment period (Visits 2 through 9) will be analyzed. Investigators will be reminded to evaluate the start and end date of exacerbations with accuracy, assessing the date when all the criteria for exacerbation were met, and the date when a subject report that their symptoms have subsided (which will not coincide with the start and end date of antibiotic prescription in all cases).

7.3.8. Rescue Medication Use

The frequency of rescue medications uses over the 24-week treatment period (Visits 2 through 9) will be analyzed per subject. Rescue medications include SABAs, SAMAs, newly prescribed LABAs, LAMAs, and oxygen (refer to Table 5).

7.3.9. Healthcare Resource Utilization

Healthcare resource utilization for pulmonary exacerbation over the 24-week treatment period (Visits 2 through 9) will be assessed per subject. Health care resource utilization will be measured by hospitalizations, including days in the hospital and days in intensive care units.

7.4. Bronchiectasis Severity Index

7.4.1. Bronchiectasis Severity Index Calculation

Bronchiectasis severity index is a scoring system based on a combination of clinical, radiological and microbiological features that can be used to assess subjects' NCFBE severity. The BSI was validated in 1,310 subjects across 5 European bronchiectasis centers. The BSI has been shown to give excellent predictions of mortality and hospital admissions and be predictive of exacerbations and QOL giving a broad assessment of disease severity (Chalmers et al, 2014).

The BSI score will be calculated at Baseline and documented in the study source document and eCRF. The actual BSI score calculation is described in Appendix 2.

7.5. Other Study Assessments

7.5.1. Medical History

Relevant medical history will be obtained from each subject at Visit 1 (Screening) and documented in the study source document and eCRF. Relevant medical history will include ongoing medications, comorbidities, and other historical diseases or treatments determined to be clinically significant in the opinion of the Investigator. During the study, any new medical information deemed relevant to medical history by the Investigator will be documented in the study source document and eCRF.

7.5.2. Smoking History and Status

The smoking history and status for each subject will be obtained at each study Visit (1 through 10).

Subject smoking history will be evaluated and grouped into three categories based on their response to the following; Current Smoker, Former Smoker, and Never Smoker (CDC-NCHS, 2017).

Subjects who report smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, smoke either every day or occasionally are defined as a Current Smoker. Subjects who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, do not smoke at all are defined as a Former Smoker. Subjects who report never having smoked 100 cigarettes are defined as Never Smoker. Subjects who are determined to be Current Smokers at Visit 1 (Screening) are not eligible for participation in the study and will be added into the eCRF as a screen failure.

For subjects who are Former Smoker or Current Smoker, their smoking history will be assessed using the number of pack-year criteria.

The pack-year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year. Subject smoking history will be documented into the study source document and the eCRF.

7.5.3. Body Mass Index

The BMI for each subject will be obtained at Visit 1 (Screening) only.

The BMI is a value derived from the mass (weight) and height of an individual subject. The BMI is calculated as the body mass (kilogram) divided by the square of the body height (meter), and is expressed in units of kg/m^2.

7.5.4. Computed Tomography Scan

Subjects who were diagnosed to have NCFBE but unable to provide the radiological report or their historical chest radiographic image are required to have a chest CT scan at Visit 1 (Screening) to confirm the diagnosis and severity of their NCFBE (refer to Table 6).

7.5.5. Concomitant Medications and Procedures

The status of each concomitant medication (ie, pre-existing or new) will be documented in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dose, regimen and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Review and documentation of prior and concomitant medications for each subject will be collected from Visit 2 (Baseline, Day 1) through Visit 10 (EOS, Day 197), and recorded in the study source document and eCRF. At each visit, the Investigator will assess if the concomitant medications the subject is taking are part of the original maintenance/reliever medications for NCFBE or whether the subject has started taking additional concomitant medications. The following information must be recorded in the eCRF for each of the medications: drug name, start date, ongoing or end date, and indication.

Concomitant procedures will be collected from Visit 1 (Baseline, Day 1) through Visit 10 (EOS, Day 197). All concomitant procedures must be recorded in the study source document and eCRF. The following information must be recorded in the eCRF for each of the medical procedure: procedure name, operation date and indication.

7.5.6. Estimated Glomerular Filtration Rate

The eGFR calculation per CKD-EPI equation will be analyzed for each subject at Visit 1 (Screening) and Visit 9 (EOT).

The CKD-EPI equation described below will be used to calculate the eGFR of creatinine clearance in mL/min.

GFR = 141 × min (Scr/κ, 1) α × max (Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:

Scr is the serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr/κ or 1,
max indicates the maximum of Scr/κ or 1.

7.5.7. Child-Pugh Score

The Child–Pugh score is used to assess the prognosis of chronic liver disease. The score employs 5 clinical measures of liver disease. Each measure is scored 1 to 3, with 3 indicating most severe derangement.

The Child-Pugh score will be calculated for those subjects whose liver function tests are abnormal and suspected to have chronic liver disease at Visit 1 (Screening) for the study eligibility.

The Child-Pugh scoring and Child-Pugh class tables can be found in Appendix 3.

7.5.8. Total Urine Protein and Urine Creatinine Quantitation

A urine protein to creatinine ratio test will be performed by the study designated central laboratory for those subjects who are suspected by the Investigator of having renal function deterioration during the study. If the ratio exceeds the normal value, a repeat sample will be taken the next day or as soon as possible. If the ratio remains elevated, it should be considered a positive result.

Instructions for collection, storage, and shipment of the urine samples will be provided in the clinical laboratory manual.

7.6. Pharmacokinetic Variables

7.6.1. Pharmacokinetic Sampling

A PK sub-study will be conducted at a select number of sites. A maximum of 36 subjects who enroll in the selected sites will undergo intensive PK sampling. The PK samples will be collected through an indwelling catheter into vacutainers with K_2EDTA prior to first dose of the study drugs in the morning at Visit 2 (Day 1) and at 1, 2, 3, 4, 6, and 8 hours post-dose, and prior to the morning dose during Visit 4 and at 1, 2, 3, 4, 6, and 8 hours post-dose on that visit day; a collection time window of ± 10 minutes will be permitted at each time point. 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). In addition, a trough PK sample (pre-dose of INS1007) will be collected at Visits 3, 6, and 9 and a PK sample will be collected pre-dose at Visit 10. For subjects who participate in the PK sub-study only, the visit window on Visit 4 will be ± 5 days. Before intensive PK sampling is conducted, the site staff will review the dosing diary to confirm that the subject has taken their study drug daily for the last 5 days. If a dose is missed in the last 5 days, the subject should have another visit arranged within the next 5 days for the intensive PK sampling once the minimum 5-day dosing requirement has been fulfilled. 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. One PK sample will be collected at 3 visits (Visits 4, 6, and 9). The details of the PK sampling scheme are described in Appendix 4.

All subjects will be advised to do their best to take their study drug around the same time every day. Approximately 5 mL of blood for the PK sample will be collected at each PK sampling time point.

Pharmacokinetic samples will be analyzed in batches on an ongoing basis, and drug concentration data will be analyzed and reviewed as a component of both the periodic internal safety and DMC reviews to confirm that INS1007 subject exposures are within the expected ranges.

Detailed instruction for PK sample collection, processing, labeling, storage, and shipping will be provided in a PK manual.

7.7. Safety Variables

Safety variables to be assessed in this study include vital signs, physical examinations, ECGs, hematology and blood chemistry values, dental examination and AEs.

7.7.1. Vital Signs

Vital signs will include BP, HR, RR, and T. Vital signs will be performed after the subject is resting at sitting or semi-recumbent position for at least 5 minutes at Screening and every study visit (Visits 1 through 10) as specified in Table 6. Vital signs will be recorded in the study source document and eCRF.

7.7.2. Physical Examination

A complete physical examination will be performed at Visit 1 (Screening), Visit 6, Visit 9, and Visit 10 (refer to Table 6).

The findings of each examination will be recorded on the study source document and eCRF. Any clinically significant abnormalities observed at Visit 1 will be recorded as medical history. Any clinically significant abnormalities not present at Visit 1 or deterioration of the conditions at Visit 1 will be recorded as AEs. The physical examination will include: weight (Visit 1 and Visit 9 only) and height (Visit 1 only), general appearance, head, eyes, ears, nose and throat, dental, respiratory, cardiovascular.

Although the evaluation of gingiva, teeth, and skin (especially on palms and soles) is considered a part of the physical examination, it is of special interest for this study, and these areas will be examined at each visit and monitored closely throughout the study. Any findings in these areas will be considered AESIs in this study (see Section 8.3).

7.7.3. Electrocardiogram

A 12-lead ECG will be performed after the subject has been resting for at least 5 minutes in semi-recumbent or supine position at Visit 1 (Screening), Visit 2 (Baseline), Visit 3, Visit 4, Visit 5, Visit 7, and Visit 9 (refer to Table 6).

The date and interpretation (normal; abnormal – not clinically significant; abnormal – clinically significant) must be recorded within the ECG page of the eCRF. Any abnormal – clinically significant findings at Baseline (Visit 2, Day 1) and any changes from Baseline prior to first dose at Visit 2 must be recorded in the medical history/current medical conditions pages of the eCRF. Any abnormal – clinically significant findings made after the Baseline visit (Visit 2) that meet the definition of an AE must be recorded on the AE page of the eCRF.

7.7.4. Clinical Laboratory Tests

Clinical laboratory tests of hematology, blood chemistry and urinalysis will be performed via the study designated central laboratory at Visit 1 (Screening) and all study Visits 2 through 10 (refer to Table 6). Clinical laboratory blood samples should be collected in the fasted state if possible after at least 4 hours without food. The clinical laboratory test parameters are listed in Table 7.

Additional safety laboratory samples may be collected if clinically indicated at the discretion of the Investigators. All retests are preferably to be done by the study designated central laboratory. However, in case of any safety concerns and urgency, the Investigator may decide to perform the retest locally per the local rules. If a retest is done locally, the date, time of retesting and results (values, units and reference ranges) will be recorded in the study source document.

Hepatitis B surface antigen (HBsAg), HIV and HCV antibody tests will be performed at Visit 1 (Screening) only via the study designated central laboratory.

Urinalysis will be performed using urine dipsticks with mid-stream clean catch urine samples.

Instructions for collection, storage and shipment of clinical laboratory samples will be provided in the clinical laboratory manual provided in the site study binder.

Table 7: Clinical Laboratory Assessments

Hematology	**Blood Chemistry**	**Urinalysis**	**Special Tests**
RBC Count	Sodium	**Dipstick**	HIV
Hemoglobin	Potassium	pH	HBsAg
Hematocrit	Calcium	Specific Gravity	HepC Ab
Mean Corpuscular Volume	Chloride	Protein	Serum Pregnancy Tests
Mean Cell Hemoglobin	Blood Urea Nitrogen	Glucose	C-Reactive Protein
Mean Corpuscular Hemoglobin Concentration	Creatinine	Ketone	
CBC With Differential	Glucose	Hemoglobin	Prothrombin Time
Platelet Count	Total protein	Bilirubin	
	Albumin	Urobilinogen	
	Alkaline Phosphatase	Nitrite	
	Creatinine Kinase		
	Total Bilirubin	Leucocytes	
	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase	Urine Protein to Creatinine Quantification and Ratio Calculation*	
	Alanine Aminotransferase	U-Protein*	
	Uric Acid	U-Creatinine*	
	LDH		
	Cholesterol		
	Triglycerides		
	Serum Bicarbonate		

*Urine protein and creatinine quantification and ratio calculation will only be performed when a subject is suspected to have renal injury per PI discretion.

CBC = complete blood count; HBsAg = hepatitis B surface antigen; HepC Ab = hepatitis C antibody; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; RBC = red blood cell.

7.7.4.1. Pregnancy Test and Reproductive Precautions

A serum pregnancy test will be performed on WOCBP at Visit 1 (Screening). A urine pregnancy test will be performed on WOCBP at Visit 2 (Baseline, prior to first dose), Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 (EOT) and Visit 10. Subjects who have a positive pregnancy test at screening are not eligible for participation in the study and will be added into the eCRF as a screen failure.

Urine pregnancy test kits will be obtained by sites locally. Pregnancy test for human chorionic gonadotropin should have sensitivity ≤ 25 mIU/mL.

In the repeat-dose toxicity studies in dogs, testicular toxicity was noted. Fertility studies in rat showed no effect on fertility in male and female rats. In embryofetal developmental toxicity studies minor malformations and variations were noted in the offspring at maternal doses that resulted in slight maternal toxicity in rats, but no embryo-fetal toxicity was noted in rabbits. INS1007 effects on fertility and fetus in human are unknown. Therefore, extreme precaution should be taken for birth control during the study.

7.7.5. Dental Examination

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 but none of the exclusion criteria except the dental 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 by the study designated local dentist (preferably a periodontist) during Visit 1 (Screening). Subjects who have the images of a full-mouth dental radiography that are performed within 6 months of Visit 1 (Screening) and available for review at Visit 1 are not required to have another dental radiography done during Visit 1. Periodontal disease will be evaluated using the Loe and Silness Gingival Index and a categorical evaluation of bleeding on probing (yes/no).

Subjects who have severe periodontitis at Visit 1 are not eligible for the study. Severe periodontitis in this study is defined as "loss of clinical attachment and probing depth ≥ 6 mm on 2 or more teeth" (Section 4.1.2, exclusion criterion 30). The entry criteria in the study have been defined to exclude subjects with underlying severe periodontal conditions that could impair the ability to detect a potential safety signal or might put the subject at increased risk. Subjects who are eligible for the study will have a dental deep cleaning (scaling and root planning) before Visit 2 (Randomization).

Subjects who are considered a screen failure for reasons not related to the dental exclusion criteria (Section 4.1.2, 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.

During the study:

NOTE: Any subject found to have developed periodontal disease or worsening gingivitis during the study will receive standard of care by a qualified dentist/periodontist.

- At each study visit, the Investigator will perform an oral soft tissue and periodontal exam to assess oral infection, gingivitis and periodontitis. The Investigator will also question whether the subject has had any bleeding, pain or swelling of the gum tissue.
- If there are any signs or symptoms of oral infection, gingivitis or periodontitis or deterioration of the pre-existing conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to the 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's discretion until end of the study.
- At Visit 5 (Week 8) and Visit 9 (Week 24), with a window of ± 7 days to complete, an oral soft tissue and periodontal examination and gum pocket measurements will be performed by a periodontist or dentist. Any site that has additional 2 mm or more in pocket depth will be re-measured along with attachment level measurement.
- If found to have progressed on the average of the 2 measures, the area will be scaled (rescue therapy).
- If more than 3 areas have progressed or if the subject has more than 2 teeth with pocket depth of ≥ 6 mm, then the study drug will be discontinued. The subject will be monitored during the remainder of their study time.
- If the subject has completed their last visit, they will be seen after an additional month to determine if the progression of periodontal disease has stopped.

7.7.6. Dermatological Assessment

The entry criteria in the study have been defined to exclude subjects with underlying dermatologic conditions that could impair the ability to detect a potential safety signal or might put the subject at increased risk. Specifically, the relevant exclusion criteria are:

- Have hypothyroidism, or myxedema, or chronic lymphedema, or acrocyanosis, or livedo reticularis. If a subject has hypothyroidism but is currently being treated, and TSH and/or T3/T4 are within normal ranges, the subject is allowed into the trial.
- Have psoriasis or lichen planus
- Have Reiter's disease/keratoderma, or blennorrhagicum, or "reactive arthritis"
- Have pityriasis rubra pilaris, or atopic dermatitis, or chronic hand dermatitis, or chronic contact dermatitis, or chronic dermatophytosis
- Have chloracne, or extensive verruca vulgaris, or keratoderma climactericum
- Perform extreme running or swimming, or other chronic, repetitive mechanical or water damage to plantar epidermis
- Are taking concomitant medications that may cause hyperkeratosis (TNF-α antagonists)

During the study:

- At each study visit (Visits 3 through 10), the Investigator will perform a careful skin evaluation, especially of the palmar and plantar surfaces, the dorsal surfaces of the

hands and feet, the Achilles tendon area, knees, and elbows. If there are any signs or symptoms of hyperkeratosis or erythema or deterioration of the pre-existing 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 the end of the study.

Any early and localized changes in the epidermal layer of skin such as scaling or thickening with minimal symptoms, in the absence of bullae and purpura, should be evaluated again in 1 week, and sooner if there are substantial changes.

Skin exfoliation or signs of skin thickening in the palms, soles, dorsum of the hands and feet, Achilles tendon area, knees, or elbows should always warrant evaluation by the dermatologist.

Discontinuation decisions will be made by the Investigator after consulting with the dermatologist. Upon receiving the dermatologist's evaluation, the Investigator should decide whether to continue the subject in the study or initiate early discontinuation of the subject.

8. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol (Section 8.1 and Section 8.2, respectively).

8.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product or not.

Examples of AEs include 1 of the following or a combination of 2 or more of these factors:

- A new sign, symptom, illness, or syndrome
- Worsening of a concomitant illness
- An effect of IP, including comparator or concomitant medication
- An effect of an invasive procedure required by the protocol
- An accident or injury

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs if the condition was known before the start of study treatment. In these cases, the condition should be reported as medical history.

8.2. Definition of a Serious Adverse Event

An SAE (experience) or reaction is any untoward medical occurrence that at any dose:

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

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A list of SAEs observed in subjects treated with IP in clinical studies of INS1007 is provided in the IB. Investigators should reference the current IB when assessing the expectedness of adverse reactions for reporting to Health Authorities/IRB/Independent or Institutional Ethics Committee (IEC)/Investigators.

8.2.1. Assessment of Intensity

Each AE will be graded per National Cancer Institute's (NCI) Common Terminology Criteria of Adverse Event version 4.0 (CTCAE v4.0). All other laboratory and clinical AEs that occur in a subject will be assessed for severity and classified using the categories below.

- **Grade 1 (Mild):** Event requires minimal or no treatment and does not interfere with the subject's daily activities.
- **Grade 2 (Moderate):** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe):** Event interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Life threatening):** Any adverse drug experience that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that had it occurred in a more severe form, might have caused death).
- **Grade 5 (Death):** The Investigator who identifies an AE will determine the causality of each AE based on the temporal relationship to administration of study drug and clinical judgment. The degree of certainty about causality will be graded using the categories below.

8.2.2. Assessment of Causality

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

- **Definitely Related:** A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; that disappears or decreases on cessation or reduction in study drug dose; and/or that reappears or worsens when the study drug is administered.
- **Probably Related:** A reaction that follows a reasonable temporal sequence from administration of study drug or that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.
- **Possibly Related:** A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by several other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.
- **Not Related:** A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

8.2.3. Assessment of Outcome

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

8.3. Adverse Events of Special Interest

8.3.1. Hyperkeratosis

The subjects' skin will be closely monitored throughout the study, especially palms and soles, dorsum of the hands and feet, Achilles tendon area, knees, and elbows. Subjects will be advised to self-monitor their skin, including skin exfoliation, and report any findings.

If there are any signs or symptoms of hyperkeratosis or erythema or deterioration of the pre-existing 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 the end of the study.

Any early and localized changes in the epidermal layer of skin such as scaling or thickening with minimal symptoms, in the absence of bullae and purpura, should be evaluated again in 1 week, and sooner if there are substantial changes.

- Discontinuation decisions will be made by the Investigator after consulting with the dermatologist. Upon receiving the dermatologist's evaluation, the PI should decide

whether to continue the subject in the study or discontinue such subject early. As a guidance, the following are events, including but not limited to, those that should trigger a dermatological evaluation:

- Signs of skin thickening in the palms, soles, dorsum of the hands and feet, Achilles tendon area, knees, or elbows.
- Skin exfoliation

8.3.2. Periodontitis/Gingivitis

Subjects' oral soft tissue, gingiva, and tooth mobility will be closely monitored at each study visit (Visits 3 through 10). Subjects will also be advised to conduct self-monitoring of their oral soft tissue, gingiva, and tooth mobility, and report any findings.

Occurrence of gingivitis or periodontitis or tooth loosening during the study will be considered an AE and reported the same as other AEs. However, in the case of a severe periodontitis/gingivitis judged by the Investigator to be study drug-related, subjects will be discontinued from the study.

8.3.3. Other Infections

Subjects will be monitored throughout the study for potential infections. Occurrence of infection will be considered an AE and reported the same as other AEs. In the case of a serious infection defined as life-threatening, requiring hospitalization, or requiring treatment with IV antibiotics, subjects will be discontinued from the study.

Note: Pulmonary exacerbations do not fall into this AESI category.

All serious infections and all specific infections believed to be associated with neutropenia, such as soft tissue infection and urinary tract infection should be entered in the infection module of the eCRF.

When a urinary tract infection is suspected, a urine culture should be performed for confirmation.

8.4. Reporting Requirements

8.4.1. Period of Observation for Adverse Events

For the purposes of this study, the period of observation for collection of any AEs will be from the time the subject signs the ICF until 30 days after the final dose of study drug or to the date of subject's EOS Visit, whichever date is later. All AEs will be followed until the resolution or stabilization of the AEs. All AEs should be recorded on the AEs Form of the eCRF and should be observed until the resolution or stabilization of the AEs. In the safety analysis, 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 summarized as medical history and not as a TEAE unless the event meets the definition of an SAE as defined below.

8.4.2. Serious Adverse Events

All SAEs, regardless of causality, must be reported to Prime Vigilance on a SAE Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 48 hours. Study-specific SAE reporting instructions will be provided in a separate SAE reporting manual.

Unexpected drug-related SAEs as assessed by Sponsor or authorized person qualify for expedited reporting and will be reported to the IRB/IEC, regulatory authorities, participating Investigators and, if cross reporting is required for suspected unexpected SAEs, to other studies/countries as well. Deaths and life-threatening events with any possible relationship to a study intervention must be reported to the Regulatory Agencies by telephone or fax as soon as possible, but within 7 calendar days of notification to Insmed. This initial report must be followed by a more complete written report within 15 calendar days. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the Regulatory Agencies in the Investigational New Drug annual report and the Drug Safety Update Report, as appropriate.

8.4.3. Hy's Law

Hy's law is a rule of thumb that a drug is at high risk of causing a fatal drug-induced liver injury when given to a large population if it caused cases of liver injury that satisfied certain criteria when given to a smaller population. If a subject has elevation of AST or ALT $\geq$ 3x ULN together with total bilirubin (TBL) $\geq$ 2 ULN without any other reason that can be found to explain the combination of increased AST/ALT and TBL during the treatment, it will be considered a Hy's law case, and needs to be reported as a SAE. The study drug administration should be discontinued.

Please refer to Appendix 5 for further instruction on cases of Hy's law.

8.4.4. Other Reportable Events

8.4.4.1. Pregnancy

Although pregnancy itself is not considered an AE, any pregnancy, including the pregnancy of a male subject's female partner, that occurs after the subject has signed the ICF and occurs during

any phase of the study must be reported to Prime Vigilance within 24 hours of learning of the pregnancy using the Clinical Study Pregnancy Form.

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

8.4.4.2. Overdose

An overdose is defined as a dose greater than the dose assigned to a subject in this study as described in Section 5.1.1. An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires an expedited reporting as if it is an SAE. In the case of an overdose, the Investigator should use clinical judgment in treating the overdose, and inform the Sponsor immediately. The Investigators should refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the IP used in the study. Such documents may include, but are not limited to, the IB of the IP.

8.5. Follow-Up of Serious Adverse Events

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

8.6. Regulatory Aspects

The Sponsor has a legal responsibility to notify the FDA, National Competent Authorities and Central Ethics Committees of the European Union, and all other foreign regulatory agencies, as well as all sites, about the safety of the drug. The Investigator has the responsibility to notify the local Ethics Committee about SAEs.

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

9. STATISTICAL METHODS

9.1. 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.

9.2. Randomization and Stratification

The randomization numbers will be assigned per the subject numbers and will be generated by the INC Research statistician in consultation with an Insmed in-house statistician.

The randomization will be stratified based on whether:

1. the sputum culture at Screening is positive for *Pa* and
2. the subject is on maintenance use of macrolides.

The randomization will be designed to ensure that the treatment arms are balanced within the PK sub-study, sparse PK subjects and 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.

9.3. Analysis Populations

9.3.1. Intent-to-Treat Population

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

9.3.2. Per-Protocol Population

All subjects who are randomized and completed the study without any major deviations will be included in the per protocol (PP) analysis.

9.3.3. Safety Population

All subjects who received at least 1 dose of the study drugs will be included in the safety analysis.

9.3.4. Pharmacokinetic Population

The PK population will consist of all subjects who receive the IP and have at least 1 measurable plasma concentration.

For the non-compartmental PK analysis, if any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis, but the data will be presented in the subject listings.

9.3.5. Pharmacodynamic Population

All subjects who received at least 1 dose of the study drugs, have at least 1 pre-dose and 1 post-dose measurement for NE, or proteinase 3, or cathepsin G, or other biomarkers, and have no major protocol deviations that considered to impact on the analysis of the PD data, will be included in PD analysis.

For the calculation of maximum inhibition and time to maximum inhibition for NE, or proteinase 3, or cathepsin G, or other biomarkers, if any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis, but the data will be presented in the subject listings.

The available PD data for any subjects excluded from the PD analysis set will be presented in subject listings only. Only subjects in the PD analysis set will be included in the descriptive summary tables.

9.4. Demographics and Baseline Characteristics

Demographic information will include date of birth, gender, ethnicity, and race. Demographics, baseline characteristics and disposition will be summarized descriptively by each treatment arm, and for the entire safety and PK populations. Height and weight, which are considered baseline characteristics and documented as part of the physical examination performed at Screening, and at the EOT (weight only), will be reported with the demographic information listed above.

9.5. Statistical Analysis

9.5.1. Efficacy and Safety

A detailed statistical analysis plan (SAP) for efficacy and safety along with their reporting will be developed. The SAP will be finalized and approved by signature prior to the database lock to preserve the integrity of the statistical analysis and study conclusions.

9.5.1.1. Efficacy Analysis

The overall significance level is set at a one-sided 0.10 to demonstrate the superiority of INS1007 to placebo.

The first step is to test INS1007 25 mg against placebo at the one-sided 0.10 level for the primary analysis and if statistically significant, INS1007 10 mg will be tested against placebo at the one-sided 0.05 level for the primary analysis.

If INS1007 25 mg is not statistically significant against placebo for the primary analysis, no further hypothesis testing will be conducted.

If only INS1007 25 mg is statistically significant against placebo for the primary analysis, then the four secondary endpoints at the INS1007 25 mg dose will be tested against placebo and the type I error rate will be controlled at the 1-sided alpha level of 0.05 using the Holm-Bonferroni method.

If both doses are statistically significant against placebo for the primary analysis, then the 4 secondary endpoints at the INS1007 25 mg dose will be tested against placebo and the type I error rate will be controlled at the 1-sided alpha level of 0.05 using the Holm-Bonferroni method and the 4 secondary endpoints at the INS1007 10 mg dose will be tested against placebo and the type I error rate will be controlled at the 1-sided alpha level of 0.05 using the Holm-Bonferroni method.

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

9.5.1.2. Primary Endpoint Analysis

The primary analysis will include ITT population. A secondary analysis will include the PP population excluding subjects with major protocol violations.

The primary efficacy endpoint is the time to the first pulmonary exacerbation over the 24-week treatment period. Any pulmonary exacerbation in the study between Visits 2 through 10 will be accounted for 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 treatment.

The efficacy analysis of the time to the first exacerbation will be performed for the ITT population using Kaplan Meier curves. The treatment comparison will be made using the stratified log rank test for the ITT population. The stratification will include the stratification factors used for the randomization. The time to the first exacerbation will also be analyzed using Cox regression model to estimate hazards ratio.

A supportive analysis of the primary efficacy endpoint will be performed for the PP population using the same methods as for the ITT population.

The exacerbation rate will be analyzed for the ITT population stratified by *Pa* colonization status and maintenance use of macrolides at Baseline.

For the primary objective, alpha will be controlled using a hierarchical testing procedure testing the high dose against placebo first and then, if statistically significant, testing the low dose against placebo. If for the primary analysis only 1 dose is statistically significant, the alpha will be split, and the secondary endpoints will be tested only for the statistically significant dose. Alpha will be controlled for the secondary endpoints using the Holm-Bonferroni method.

The analysis of the primary endpoint and the reporting will be described in more detail in the SAP.

9.5.1.2.1. Secondary Endpoints Analysis

Secondary endpoints of QOL-B, FEV_1, and NE will be analyzed using analysis of variance; the rate of pulmonary exacerbations will be analyzed using Cochran-Mantel-Haenszel statistics and will be described in more detail in the SAP.

9.5.1.2.2. Exploratory Endpoints Analysis

The analysis of the exploratory endpoints and their reporting will be described in more detail in the SAP.

9.5.1.3. Safety Analysis

All safety data will be summarized by treatment received (which may differ from the randomized treatment arm) and for the entire safety population using descriptive statistics.

Subject disposition will be listed and summarized including the number of withdrawals and the primary reason for withdrawal. Subjects excluded from any analysis sets will be listed including the reasons for exclusions.

All safety data will be listed for each subject and summarized appropriately. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Additional summaries by severity (NCI CTCAE) and relationship to study treatment will be presented.

All clinical safety laboratory data and vital signs will be listed and summarized including changes from Baseline. Any out of range laboratory measurements will be flagged in the listings.

Digital ECG (dECG) data will be smoothed, and the HR and QTcF will be derived from the smoothed data at each time point. The dECG data will be listed and summarized descriptively; outlier analyses for QTcF will also be performed.

The analysis of the safety endpoints and their reporting will be described in more detail in the SAP.

9.5.1.3.1. Adverse Events

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

The number and percent of subjects with AEs will be presented by treatment and dose group. The severity of AEs, the relationship to IP, AEs causing study discontinuation, and SAEs will be similarly presented. All AEs reported during the study will be listed. Treatment emergent and

treatment-related AEs will be tabulated by body system and organ class. Placebo from all treatments will be pooled and described.

9.5.1.3.2. Clinical Laboratory Tests

The results of hematology, blood chemistry, and urinalysis will be listed for each subject. Laboratory values outside the normal ranges will be flagged. If applicable, summary statistics (mean, range, change from Baseline) by treatment will be provided for each time point. Baseline is defined by laboratory values from blood and urine samples collected prior to first dose during the Baseline visit. Summary statistics of clinical laboratory values will be tabulated by treatment and dose.

9.5.1.3.3. Vital Signs

Systolic and diastolic BP, HR, RR, and T will be listed for each subject. If applicable, summary statistics (mean change, percentage change from Baseline, and absolute change from Baseline) by treatment at each time point will be provided. Baseline is defined by vital signs collected prior to first dose on Day 1.

9.5.1.3.4. Physical Examination

Post-Baseline findings of the physical examinations that meet the criteria of AEs will be listed in the relevant AE listings.

9.5.1.3.5. Electrocardiogram

The results of the safety ECG will be listed for each subject. Post-baseline findings of the ECG results that meet the criteria of AEs will be listed in the relevant AE listings. If applicable, summary statistics of ECG results will be provided.

9.5.2. Pharmacokinetic and Pharmacodynamic Analysis

9.5.2.1. Pharmacokinetic Analysis

For subjects participating in the PK sub-study, plasma concentrations of INS1007 will be listed and summarized by dose level of INS1007 over each scheduled sampling time using descriptive statistics (including arithmetic mean, SD, median, minimum and maximum, geometric mean, and percent coefficient of variation of the geometric mean, as appropriate). Individual plasma concentration data versus time will be presented in data listings, along with graphical plots of individual and geometric mean plasma concentration-time plots presented in linear and semi-logarithmic scale.

The main PK endpoints will be the following plasma PK parameters derived using non-compartmental principles using Phoenix™ WinNonlin® (Certara, Princeton NJ): C_{max}, C_{ss}, C_{maxss}, C_{minss}, t_{max}, $t_{max,ss}$, AUC_{0-8}. Other additional PK parameters may be estimated and/or reported.

Plasma PK parameters will be listed and summarized using descriptive statistics, as appropriate.

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. INS1007 plasma concentration

data from this study will be pooled with data from other studies for the purposes of developing a population PK (PPK) model. After an adequate structural model is identified, co-variate analysis may be performed to evaluate the effect of intrinsic and extrinsic factors on the PK model parameters.

Actual sampling times and INS1007 plasma concentrations from sparse sampling will be listed but not summarized. The modeling output will be reported outside of the clinical study report (CSR).

A detail SAP for the PK parameters and reporting will be developed. The PK SAP will be finalized and approved by signature prior to the database lock to preserve the integrity of the statistical analysis and study conclusions.

9.5.2.2. Pharmacodynamic Analysis

Pharmacodynamic parameters that are planned to be analyzed are NE, proteinase 3, cathepsin G, ANC and other biomarkers (eg, MOP, interleukin 8 [IL-8], regulated on activation, normal T-cell expressed and secreted [RANTES], TNF-α, interleukin 1 beta [IL-1β], leukotriene B4 [LTB-4], monocyte chemotactic protein 1 [CCL2] [MCP-1], interleukin-6 [IL-6], S100A12, MMP8, and MMP9).

The results of NE, proteinase 3, cathepsin G activities, ANC, and other biomarkers will be listed by subject and time point. Note that ANC will be included in both safety and PD-related analyses.

The time to maximum inhibition and maximum inhibition for NE, proteinase 3, cathepsin G activities, and ANC will be calculated and listed for each subject.

The NE activity in sputum and blood will be calculated as percent inhibition from the pre-treatment activity and normalized by ANC (blood only). Pre-treatment value is defined as the mean value of NE activities at Screening and Baseline and will be listed and summarized together with the ANC measurements.

Descriptive statistics for NE, proteinase 3, cathepsin G activities, ANC, and derived activity parameters (maximum inhibition and time to maximum inhibition) will be presented by dose levels of INS1007 and placebo.

Individual figures of NE, proteinase 3, cathepsin G activities and ANC versus time will be presented with all subjects overlaid on the same plot for each dose level (spaghetti plots). Mean plots versus time will also be presented with all dose levels and pooled placebo overlaid on the same plot.

INS1007 PD data from this study will be pooled with data from other studies for the purposes of developing a PPK/PD model. Co-variate analysis may be performed to evaluate the effect of intrinsic and extrinsic factors on the PD model parameters. A stand-alone Modeling and Simulation analysis plan will be written for the PK/PD and PD models. The modeling output will be reported outside of the CSR.

9.5.2.3. Pharmacokinetic-Pharmacodynamic Analysis

The relationship between INS1007 exposure and PD mechanistic markers of DPP1 inhibition (ie, NE, proteinase 3 and cathepsin G levels, or other biomarkers (eg, ANC, MOP, IL-8, RANTES,

TNF-α, IL-1β, LTB-4, MCP-1, IL-6, S100A12, MMP8, and MMP9), will be explored graphically. If appropriate, linear or nonlinear models may be used to further describe the relationship between INS1007 and PD biomarkers.

In addition to the PK-PD analysis, other analysis methodologies, such as nonlinear mixed-effect modeling, may be employed to further characterize the PK/PD relationship of INS1007.

9.5.2.4. Pharmacodynamic-Pharmacodynamic Analysis

The relationship between INS1007 PD biomarkers of DPP1 inhibition (eg, NE, proteinase 3, and cathepsin G levels) and outcome measures (ie, pulmonary exacerbation, FEV_1, etc.) or other biomarkers (eg, MOP, IL-8, RANTES, TNF-α, IL-1β, LTB-4, MCP-1, IL-6, S100A12, MMP8, and MMP9) will be explored graphically. If appropriate, linear or nonlinear models may be used to further describe their relationship.

In addition to the PD-PD analysis, other analysis methodologies, such as nonlinear mixed-effect modeling, may be employed to further characterize the PD/PD relationship of INS1007.

9.6. Interim Analysis

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

9.7. Sample Size Reassessment

A blinded sample size reassessment is planned for this study. This assessment will compare the observed exacerbation rate to assumed background exacerbation rate. 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. This analysis is not intended to change any aspect of the protocol other than possibly increasing the sample size. The sample size will be reassessed when up to 70% (n = 168) of the randomized subjects have completed study treatment.

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 subjects with an event, or 61 subjects with an event, 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 subjects with an event once 70% (n = 168) of the randomized subjects on trial have completed study treatment, 61 is the number of subjects with an event 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.

10. DATA INTEGRITY AND QUALITY ASSURANCE

10.1. Source Documents

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

10.2. Data Collection and Case Report Form Monitoring

All data obtained for this study will be entered in a Code of Federal Regulations Title 21 (21 CFR) Part 11-compliant Data Management System provided by Insmed or its designee. These data will be recorded with an electronic data capture (EDC) system using eCRFs. The Investigator will ensure the accuracy and completeness of the data reported to the Sponsor. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

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

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

10.3. Study Records Retention

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

11. ETHICAL CONSIDERATIONS, COMPLIANCE STATEMENT AND REGULATORY COMPLIANCE

11.1. Ethical Considerations

A copy of the protocol, ICFs, other information to be completed by subjects, such as questionnaires and any proposed advertising or recruitment materials, will be submitted to the regulatory authority(ies) and ECs.

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

Periodic study status reports, as applicable, will be submitted to the ECs in accordance with country specific regulations. The PI will be responsible for obtaining EC approval of the annual continuing review throughout the duration of the study.

The PI will notify the local ECs of violations from the protocol and SAEs.

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

11.2. Good Clinical Practice

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (October 2013), the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and FDA GCP Regulations: C21 CFR, Parts 11, 50, 54, 56, and 312 as appropriate.

The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements as applicable. Throughout the study, the Sponsor and its designee will work with the Investigator(s) to ensure proper study protocol implementation and adherence to regulatory requirements as listed in the study protocol.

11.3. Delegation of Investigator Duties

The PI should ensure that all persons assisting with the study are adequately qualified, trained, and informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions.

The PI should maintain a list of sub-Investigators and other appropriately qualified persons to whom he/she has delegated significant study related duties.

11.4. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals regarding the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the CRF/eCRF or other documents submitted to Insmed, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not for submission to Insmed ICFs should be kept in strict confidence by the Investigator.

In compliance with federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

11.5. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject, or legally acceptable representative, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject, or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

11.6. Regulatory Compliance

Insmed has a legal responsibility to notify the FDA, national competent authorities and Central Ethics Committees of the European Union, and all other foreign regulatory agencies, as well as all sites, about the safety of the drug.

The study protocol, subject information and consent form, the IB, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC for ethical review and approval according to local regulations prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the EC and/ or Insmed for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the EC of deviations from the protocol or SAEs occurring at the site and other AE reports received from Insmed, in accordance with local procedures.

As required by local regulations, Insmed's Regulatory Affairs group will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

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

12. STUDY ADMINISTRATIVE INFORMATION

12.1. Financial Disclosure

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

12.2. Study Registration and Results Disclosure

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

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

12.3. Study Files and Materials

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

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

The study may be audited by qualified delegates from the Sponsor or a competent regulatory authority.

12.4. Use of Stored Samples and Data

As described in Section 7.6.1, plasma will be stored for PK analysis. Stored samples will be labeled with study and subject information and kept in a locked room with limited access. Electronic data will be kept in password-protected computers at the laboratory and then transferred to the Sponsor or clinical research organization (CRO), as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's tracking system.

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

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

Unless otherwise directed by the subject, at the completion (termination) of the study, samples will continue to be stored for a period of up to 2 years, or longer if required by the institution participating in the study. In all cases, samples will be stored until the completion (termination)

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

12.5. Disposition of Stored Samples and Data

Access to stored samples will be limited by using a locked room. Data will be kept in password-protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

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

Any loss or unanticipated destruction of samples (eg, due to freezer malfunction) or data (eg, loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to the Sponsor and the IRB.

At the completion (termination) of the study, samples will continue to be stored for a period of up to 2 years, or longer if required by the institution participating in the study.

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

12.6. Study Initiation

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

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

12.7. Subject Reimbursement, Liability, and Insurance

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

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

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

12.8. Subject Identification and Confidentiality

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

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

12.9. Study Monitoring

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

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

12.10. Protocol Amendments

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

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

should be informed within 10 working days. Any other regional reporting requirements must be adhered to.

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

12.11. Audits and Inspections

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

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

12.12. Publication Policy and Data Usage

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, if Insmed has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of Insmed Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of the study Sponsor. Authorship will be determined by agreement.

The study Sponsor must receive copies of any intended communication in advance of publication (at least 60 working days for an abstract or oral presentation and 90 working days for a journal submission). The study Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as the study Sponsor personnel.

After study completion and comprehensive data analysis, the results of study will be described in the CSR.

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14. APPENDICES

APPENDIX 1. SPUTUM INDUCTION GUIDELINES

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

Note: If a subject is unable to produce sputum spontaneously during Screening (Visit 1), the subject will be considered a screen failure. The subject may not undergo a sputum induction procedure during Screening (Visit 1) to meet eligibility (Section 4.1, inclusion criterion 5).

Purpose

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

Required Equipment

- Standard handheld nebulizer used in the site or the subject can be asked to bring the nebulizer they use at home for pulmonary hygiene
- The nebulizer should be thoroughly disinfected to ensure no cross-contamination
- Sputum specimen containers with label – sputum collection tube provided by central laboratory
- Sodium chloride solution (saline) – 3% and 7%, and possibly 10%
- Standard clinic supplies (eg, disinfectant/germicidal/alcohol wipes, tissues, paper towels, etc)

Procedure

General Instructions:

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

Inhalation and Collection Procedures:

- The induction procedure should start by utilizing either 3% or 7% saline based on the Investigator's preference.
- Approximately 3 to 6 mL of the selected saline should be placed in the nebulizer.
- The subject should be sitting up or in a semi-Fowler position.
- The subject may wear a nose clip during the nebulization.
- The subject should breathe slowly and deeply through the nebulizer mouthpiece inhaling the salt water mist. Remind the subject not to breathe quickly but to have slow, deep breaths pausing at peak inspiration to allow deposition of particles.
- The nebulization time is 10 minutes.
- At the end of this time, the subject should take a few deep breaths, swallow the extra saliva in his/her mouth and try to cough up a sputum sample.
- The subject should be encouraged to cough forcefully using the deep coughing method and/or "huffing" cough method.
- All sputum should be deposited in the specimen container. The container should not be opened until the specimen is ready to be deposited. The container should be closed immediately after depositing the sample.
- The sputum sample should be approximately 3 mL - slightly below the bottom line (5 mL) on the collection container.
- If a sufficient sputum sample is not collected and the subject appears to be tolerating the induction procedure well, the subject can complete another 10-minute nebulization period.
  - If a second 10-minute nebulization period is required, the recommendation is to increase the sodium chloride concentration (ie, if 3% was used first then 7% should be used for the subsequent nebulization; if 7% was used first then 10% should be used for the subsequent nebulization).
  - Closely monitor the subject for tolerability issues or side effects.
  - No more than two 10-minute nebulization periods should be completed.
- The sputum sample should be refrigerated until it is sent to the microbiology laboratory.

Side Effects

- The subject may experience side effects from the sputum induction procedure. The most common side effects include:

  - coughing
  - wheezing
  - lightheadedness
  - shortness of breath
  - sore throat
  - nausea
  - headache
  - chest tightness

- Other possible side effects include hyperventilation or bronchospasm. For bronchospasm, ensure subject receives the necessary medical management.

Miscellaneous

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

APPENDIX 2. 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*.

THE MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCALE

Grade	Degree of Breathlessness Related to Activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after walking a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

APPENDIX 3. CHILD-PUGH SCORING AND CLASS REFERENCE TABLES

Child-Pugh Scoring

Measure	1 Point	2 Points	3 Points
Total Bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34 to 50 (2 to 3)	> 50 (> 3)
Serum Albumin, g/dL	> 3.5	2.8to 3.5	< 2.8
Prothrombin Time, Prolongation(s)	< 4.0	4.0 to 6.0	> 6.0
Ascites	None	Mild (or Suppressed With Medication)	Moderate to Severe (or Refractory)
Hepatic Encephalopathy	None	Grade I to II	Grade III to IV

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from the Child-Pugh Scoring Table above.

Child-Pugh Class

Points	Class	One-year survival	Two-year survival
5to 6	A	100%	85%
7 to 9	B	81%	57%
10 to 15	C	45%	35%

APPENDIX 4. INTENSE PHARMACOKINETIC SAMPLING SCHEME

Intense PK Sub-Study Blood Sampling Times and Time Windows

Visit	Collection Time Relative to Drug Administration	Collection Window
Visit 2	0 hour (pre-dose)	-30 min
	1hr	± 10 min
	2 hr	± 10 min
	3 hr	± 10 min
	4 hr	± 10 min
	6 hr	± 10 min
	8 hr	± 10 min
Visit 3	Pre-dose on the visit day	
Visit 4	Pre-dose on the visit day	-30 min
	1 hr	± 10 min
	2 hr	± 10 min
	3 hr	± 10 min
	4 hr	± 10 min
	6 hr	± 10 min
	8 hr	± 10 min
Visit 6	Pre-dose on the visit day	
Visit 9	Pre-dose on the visit day	
Visit 10	A PK sample will be collected at any time during Visit 10.	
A total of 18 PK samples will be collected from each subject.		

Note: Subjects will be reminded not to take their study drugs on the day of their visits when their PK sample(s) will be taken.
Note: A trough (pre-dose) PK sample will be collected at 3 of the 4 visits of Visits 3, 6, and 9. For visit 10, collection of PK samples can be done at any time either pre- or post-dose during the visit.
Note: A PK sample between 0.5 to 4 hours post-dose will be collected at 2 of the 4 visits of Visits 3, 4, 6, and 9.

Note: At Visits 2 and 4, subjects will be fed after the 1-hour blood draw.
PK = pharmacokinetic(s).

APPENDIX 5. HY'S LAW

During the study, the Investigators will remain vigilant for increases in liver enzymes. The Investigators are responsible for determining whether a subject meet potential Hy's law criteria at any time during the study. The Investigators together with the Sponsor physicians, will determine if Hy's law criteria are met or not. The Investigators are responsible for recording and reporting Hy's law cases per the safety reporting requirement described below.

Potential Hy's Law

A subject's AST or ALT ≥ 3× ULN and TBL ≥ 2× ULN at any time point during the treatment irrespective of any increase of alkaline phosphatase will be considered to meet potential Hy's law. The elevations of AST or ALT with TBL do not have to occur at the same time or within a specified time frame.

Hy's Law

A subject's AST or ALT ≥ 3× ULN and TBL ≥ 2× ULN at any time point during the treatment without any other reasons (such as viral hepatitis or another drug or cholestasis) other than the IP will be considered to meet Hy's law. The elevations of AST or ALT with TBL do not have to occur at the same time or within a specified time frame.

Identification of Potential Hy's Law Cases

To identify cases of potential Hy's law, it is important to perform a comprehensive review of clinical laboratory data for any subject who meets the following criteria in isolation or in combination:

ALT ≥ 3× ULN

AST ≥ 3× ULN

TBL ≥ 2× ULN

The subjects should be closely monitored. Their liver enzymes and serum bilirubin tests will be tested 2 to 3 times weekly. The frequency of the testing can decrease to once a week or less if abnormalities stabilize. The Investigators will review without any delay every new clinical laboratory reports. The Investigators should notify Sponsor if any of the above criteria are met, and determine whether the subject meets potential Hy's law. If the potential Hy's law is met, the Investigator will inform the Sponsor responsible physician who will then inform the entire Sponsor study team. The Investigator is responsible for providing the Sponsor all the available relevant data in a timely fashion for review, and will discuss with the Sponsor to determine together if there is an alternative explanation for meeting potential Hy's law other than drug induced liver injury caused by the IP. The Sponsor medical science director and global safety physician will also be involved in the data review and discussion together with other subject matter experts as appropriate to determine if Hy's law is met. The Investigator and the Sponsor will agree on an approach for the situation.

The Investigator is responsible for closely monitoring the subject until his/her liver enzyme levels and relevant signs or symptoms return to normal or at least baseline, or if medically indicated.

Per the outcome of the joint review and assessment, the Investigator will follow the instructions below:

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE. If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF. If the alternative explanation is an AE/SAE, record the AE/SAE in the AE eCRF accordingly.

If there is NO agreed alternative explanation that would explain the ALT or AST and TBL elevations other than IP, Hy's law is met and it should be reported as a SAE with the reporting term of "Hy's law" and causality assessment of "related" should be assigned.