

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217673Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 133790

MEETING MINUTES

Insmmed Incorporated
Attention: Sandy Lee
Senior Director, Regulatory Affairs, Insmmed Inc.
700 US Highway 202/206
Bridgewater, NJ 08807-1704

Dear Sandy Lee:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brensocatib (INS1007).

We also refer to the video conference between representatives of your firm and the FDA on January 17, 2024. The purpose of the meeting was to acquaint the Agency with the information to be submitted in the planned NDA, as well as the overall presentation and formatting of data. In addition, the Sponsor would like to obtain the Agency's feedback for the updated statistical analysis plan for Study INS1007-301 prior to the availability of data from the ongoing Phase 3 study. Lastly, in support of assessing pediatric safety and effectiveness of brensocatib, the Sponsor is seeking agreement regarding the timeframe for providing feedback for the deferred pediatric study in participants ≥ 6 to < 12 years old during the review of the NDA.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Ji Hyun LaRose, PharmD
LCDR, U.S. Public Health Service
Senior Program Management Officer
Pulmonology, Allergy, and Critical Care
Division of Regulatory Operations for -

¹We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 17, 2024 @ 12:00 PM – 1:00 PM EST
Meeting Location: Zoom

Application Number: 133790
Product Name: brensocatib (INS1007)

Indication: Non-Cystic Fibrosis Bronchiectasis
Sponsor Name: Insmmed Incorporated
Regulatory Pathway: 505(b)(1)

Meeting Chair: Banu Karimi-Shah, MD
Meeting Recorder: Ji Hyun LaRose, PharmD

FDA ATTENDEES

Banu Karimi-Shah, MD, Deputy Director, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Stacy Chin, MD, Clinical Team Leader, DPACC
Katherine Clarridge, MD, Clinical Reviewer, DPACC
Yunzhao Ren, MD, PhD, Master Pharmacokineticist, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Lei He, PhD, Clinical Pharmacology Reviewer, DCPH, OCP
Carol Galvis, PhD, Pharmacology/Toxicology Supervisor, Division of Pharmacology and Toxicology for Immunology and Inflammation (DPT-II)
Anup Srivastava, PhD, Pharmacology/Toxicology Reviewer, DPT-II
Yongman Kim, PhD, Biometrics Team Leader, Division of Biometrics III, Office of Biostatistics (OB)
Dong-Hyun Ahn, PhD, Biometrics Reviewer, Division of Biometrics III, OB
Ji Hyun LaRose, PharmD, Senior Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations (DRO-II/ORO)
Julienne Lee, PharmD, Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations (DRO-II/ORO)
Thomas Yung, MSN, CRNP, Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations (DRO-II/ORO)

SPONSOR ATTENDEES

Gregg Ruppertsberger, Global Commercial Lead, Brensocatib
Junguo (Joe) Zhou, PhD, DABT, Executive Director, Toxicology
Helen Usansky, MD, PhD, Senior Director, Clinical Pharmacology
Raul Villa, MD, Vice President, Drug Safety & Pharmacovigilance
Kevin Mange, MD, MSCE, Clinical Development Officer, Clinical Development
Diane Fiorenza, BS, RAC, Vice President, Regulatory Affairs
Nadejda Soukhareva, MS, Executive Director, Regulatory Affairs
Sandy Lee, MS, RAC, Senior Director, Regulatory Affairs
Carlos Fernandez, MD, Executive Director, Clinical Development
Ariel Teper, MD, Vice President, Clinical Development
Lin Wang, PhD, Vice President, Biometrics
Andrea Maes, PhD, Senior Director, Head of Biostatistics
Chunpeng Fan, PhD, Senior Director, Biostatistics
Martina Flammer, MD, MBA, Chief Medical Officer
Gene Sullivan, MD, Chief Strategy Officer
Yun (Irene) Gregan, MD, Senior Director, Clinical Development
Ralph Ceres, Executive Director, Program Management

1.0 BACKGROUND

In a submission dated November 17, 2023, Insmmed requested a meeting to acquaint the Agency with the information to be submitted in the planned NDA, as well as the overall presentation and formatting of data. In addition, the Sponsor would like to obtain the Agency's feedback for the updated statistical analysis plan for Study INS1007-301 prior to the availability of data from the ongoing Phase 3 study. Lastly, in support of assessing pediatric safety and effectiveness of brensocatib, the Sponsor is seeking the Agency's agreement regarding the timeframe for providing feedback for the deferred pediatric study in participants ≥ 6 to < 12 years old during the review of the NDA.

The meeting was granted for January 17, 2024. Insmmed's specific questions from the briefing document dated, December 18, 2023, are listed below in *italics* and the FDA responses are provided in normal font.

FDA sent Preliminary Comments to Insmmed on January 12, 2024.

2.0 DISCUSSION

Question 1:

Does the Agency have any comments to the proposed Formal Communication Plan for the review of the brensocatib NDA?

FDA Response:

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Your proposed formal communication timeline provided in the meeting package appears consistent with a priority review timeline. An application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness over available therapies. The Agency considers NCFBE a serious condition and recognizes that brensocatib has breakthrough therapy designation for this indication. We will make a determination regarding Priority Review designation at the time of NDA submission and filing based on the available safety and efficacy data. Therefore, while we have no further comments on the proposed formal communication plan, bear in mind that the NDA review timeline is subject to change based on priority review determination and other issues that may arise (e.g., AC meeting determined to be necessary). Subsequent significant changes to the planned timeline will be conveyed promptly should they arise.

Meeting Discussion:

No discussion occurred.

Question 2:

Does the Agency agree that the NDA for brensocatib can be considered for Priority Review if evidence of safety and effectiveness from the Phase 3 study is demonstrated?

FDA Response:

See FDA Response to Question 1.

Meeting Discussion:

No discussion occurred.

Question 3:

Does the Agency agree to the Sponsor's plan for providing financial disclosure certifications for only Studies INS1007-301 and INS1007-201 to support the review of the NDA?

FDA Response:

As disclosure of financial interests and arrangements is required only for covered clinical studies, specifically, those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety, your proposal to include financial disclosures for the principal investigators in Trials INS1007-301 and INS1007-201 appears reasonable. We refer you to the guidance *Financial Disclosure by Clinical Investigators*.²

Meeting Discussion:

No discussion occurred.

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/financial-disclosure-clinical-investigators>

Question 4:

Does the Agency agree to review and provide feedback for the proposed clinical study protocol (INS1007-202) for pediatric participants ≥ 6 to <12 years of age during the NDA review?

FDA Response:

Because the design of the proposed clinical protocol for pediatric subjects ≥ 6 to <12 years of age is dependent upon data gathered from the adolescent population in your pivotal study, we strongly recommend you postpone submission of the protocol for INS1007-201 until we have reviewed the adolescent data in the NDA submission. Per ICH Guideline E11A on Pediatric Extrapolation³, your extrapolation concept should include a discussion of the extrapolation of safety and efficacy and a thorough justification to support any conclusions about the acceptability to extrapolate safety and efficacy information from all the reference populations to the target population. Given the heterogeneous nature of the condition and differences in underlying etiologies and management between adult and pediatric patients, we anticipate that a Bayesian approach with justification for the degree of borrowing of adult and adolescent data from the pivotal trial will be necessary to demonstrate efficacy of brensocatic in this age group. For additional guidance, we refer you to recently published articles about Bayesian methods:

1. James Travis, Mark Rothmann & Andrew Thomson (2023): *Perspectives on informative Bayesian methods in pediatrics*, *Journal of Biopharmaceutical Statistics*, DOI:10.1080/10543406.2023.2170405
2. Ionan, Alexei & Clark, Jennifer & Travis, James & Amatya, Anup & Scott, John & Smith, James & Chattopadhyay, Somesh & Salerno, Mary & Rothmann, Mark. (2022). *Bayesian Methods in Human Drug and Biological Products Development in CDER and CBER. Therapeutic Innovation & Regulatory Science*. 57(4), DOI: 10.1007/s43441-022-00483-0.

Meeting Discussion:

No discussion occurred.

Question 5:

Does the Agency agree to review an updated PPSR submitted to IND 133790 after approval of the protocol for Study INS1007-202 during the NDA review?

FDA Response:

The content of your proposed PPSR under IND 133790 will be influenced by the adolescent data included in the initial NDA submission. Therefore, we strongly recommend you postpone the submission of the PPSR until after we have fully reviewed the available adolescent data, including the completed dataset submitted with the 120-day safety update and reached general agreement upon the pediatric study

³ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation>
U.S. Food and Drug Administration
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protocol. In addition, note that the PPSR must include any conditions in which use of brensocatib in the pediatric population may produce health benefits.

Meeting Discussion:

No discussion occurred.

Question 6:

Does the Agency agree that the proposed organization and content of the eCTD will be acceptable to file the NDA?

FDA Response:

The proposed content and structure of the NDA as detailed in the eCTD Draft Table of Contents appears consistent with the FDA eCTD technical specification *The Comprehensive Table of Contents Headings and Hierarchy*⁴ and sufficient for filing purposes. However, we may request further details at the time of review. We refer you to the guidance *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry*.⁵

Meeting Discussion:

No discussion occurred.

Question 7:

Does the Agency agree to the Sponsor's plan for providing content only for Study INS1007-301 and Study INS1007-201 for the BIMO to support the review of the NDA?

FDA Response:

Your proposal to provide content described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*⁶, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*⁷ for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials, INS1007-301 and INS1007-201) appears reasonable. If the required items are provided elsewhere in submission in the format described, you may describe the location or provide a link to the requested information.

Meeting Discussion:

No discussion occurred.

⁴ <https://www.fda.gov/media/76444/download>

⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications>

⁶ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/standardized-format-electronic-submission-nda-and-bla-content-planning-bioresearch-monitoring-bimo>

⁷ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm#guides>

Question 8:

Does the Agency agree that the proposed SDSP and programs are adequate to support the review of the NDA?

FDA Response:

You have developed a Study Data Standardization Plan (SDSP) to describe the data standardization approach for nonclinical and clinical studies to be included in your NDA submission that includes the following:

- Datasets in the SEND format for all applicable nonclinical studies that were initiated after December 17, 2016
- Summary datasets for all applicable nonclinical studies initiated prior to December 17, 2016
- CDISC-compliant datasets for all clinical studies except for D6190C00001 and D6190C00003
- SAS programs for the primary and secondary endpoints main analysis as well as the corresponding analysis dataset programs for INS1007-301

Your approach to study data standardization appears sufficient for filing purposes. In addition to guidance provided in the Final Written Responses dated August 25, 2023, we have the following general comments that pertain to data and analyses:

1. The data definition file (i.e., Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. Submit corresponding Define.pdf files in addition to the Define.xml files.
2. For the pivotal study(s), provide a table that contains the following:
 - a. Dates of first patient and last patient visits
 - b. Dates of data lock
 - c. Dates for each interim analysis
 - d. Dates of the initial protocol and all revisions with a hyperlink to the protocol and each revision; include a hyperlink to Summary of Changes for each version
 - e. Dates of all versions of the Statistical Analysis Plan (SAP) with a hyperlink to each SAP; include a hyperlink to Summary of Changes for each version and specify the number of subjects enrolled in the trial at the time of each protocol change.

3. All data for a given domain or data set (e.g., ADLB) should be contained in one dataset. The dataset should include flags to permit evaluation of the relevant analysis populations as outlined in the ISS SAP and CSR.
4. Submit a dataset that contains all subjects that were unblinded prior to data lock. The dataset should include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.
5. Include flags in the ADSL dataset to indicate if a narrative, CRF, or adjudication package has been submitted for each patient.
6. Submit a dataset or table that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication package (s). The dataset should contain four variables with an indicator for whether each item was submitted.
7. For each study, provide a flag in the AE dataset or a separate dataset that maps preferred terms to the adverse events of special interest (AESIs).
8. We recommend use of the latest version of MedDRA and WHO Drug Dictionary (2023) for upconverting the integrated datasets used in the ISS. Explain any differences in the collection of adverse event data and the definition of treatment emergent adverse events between trials.
9. You should plan to evaluate all AEs based on logical groupings of preferred terms (PTs) using standard MedDRA queries or other appropriate groupings of PTs. Include in your submission the procedures and rationale used for grouping of PTs. The intent of safety analyses based on grouped PTs is to avoid splitting of PTs so that adverse events are adequately captured (e.g., "ABDOMINAL PAIN, UPPER", "ABDOMINAL PAIN, LOWER", "ABDOMINAL PAIN" should be grouped together in the assessment for abdominal pain)

Meeting Discussion:

No discussion occurred.

Question 9:

Does the Agency agree that the nonclinical package consisting of pharmacology, DMPK, and toxicology studies is sufficient to support the review of the NDA for brensocatib for the treatment of NCFBE in adult and pediatric patients 12 years of age and older?

FDA Response:

Pending review of the ongoing carcinogenicity studies, we agree that the nonclinical package for brensocatib is sufficient to support the review of the NDA.

Meeting Discussion:

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No discussion occurred.

Question 10:

Does the Agency agree that the proposed package of combined adult and available adolescent data from Study INS1007-301 can be sufficient to support the review of the NDA for brensocatib for the treatment of NCFBE in adult and pediatric patients 12 years of age and older?

FDA Response:

Your plan to include data from all randomized adults who have completed the 52-week treatment period in Study INS1007-301 as well as all available data from the adolescent subjects aged 12 to < 18 years of age appears acceptable to support the filing of an NDA submission. The acceptability of the data and the final indication are review issues.

Meeting Discussion:

No discussion occurred.

Question 11:

Does the Agency agree that the clinical data package is acceptable to file the NDA and can be sufficient to support the review of the NDA for the treatment of NCFBE in adult and pediatric patients 12 years of age and older?

FDA Response:

We understand your initial NDA submission will include the following clinical trial data to support your proposed indication:

- Placebo-controlled efficacy and safety data from the single pivotal trial INS1007-301
- Results from the completed phase 2 dose-ranging trial, INS1007-201, a phase 2, randomized, placebo-controlled study
- Multiple phase 1 clinical pharmacology studies
- Additional supportive studies including those conducted in subjects with cystic fibrosis and CRSsNP

The clinical data package appears sufficient for filing purposes.

Meeting Discussion:

No discussion occurred.

Question 12:

Does the Agency agree with the proposed analyses provided in the updated draft SAP and the proposed changes to the multiplicity control strategy for Study INS1007-301?

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FDA Response:

- In general, the proposed analyses provided in the updated draft SAP appear reasonable. Regarding the proposed changes to the multiplicity control strategy, we strongly discourage removal of the “time to first pulmonary exacerbation” and “annualized rate of severe pulmonary exacerbations” endpoints from the multiplicity control procedure if they are to be considered for labeling claims. While the ultimate placement is at your discretion, we recommend retaining these endpoints in the testing hierarchy rather than using descriptive statistical analyses. As discussed at the end-of-phase 2 meeting on July 8, 2020, we agree with your proposal to use $\alpha = 0.01$ (two-sided) for the comparisons of the two brensocatib doses relative to placebo for the primary endpoint.
- Additionally, to assess the benefit-risk of brensocatib in NCFBE in adolescents, we strongly encourage you to explore a Bayesian approach to inform efficacy in adolescent subjects (on the primary endpoint) and therefore on the comparability of treatment effect between adolescents and adults. Adequate justification is required for a full extrapolation approach of adult data to the adolescent population.
- Provide additional justification for your proposal to decrease the interval defining separate exacerbation events from 28 to 14 days based on feedback obtained at the Antimicrobial Drugs Advisory Committee Meeting held on January 11, 2018.

Meeting Discussion:

The Sponsor clarified the reference to the Antimicrobial Drug Advisory Committee Meeting held on January 11, 2018, was provided as an example of a program in NCFBE that implemented the 14-day interval, and that there was no specific discussion or feedback obtained from this meeting that was used to justify the decrease in the interval between pulmonary exacerbation events. Additionally, the EMA suggested the sponsor reevaluate a shorter interval between pulmonary exacerbations. In response to the Agency’s request for additional justification to decrease the interval defining separate exacerbation events from 28 to 14 days, the Sponsor provided the following references and explanations:

- Different clinical programs in Respiratory, including asthma (Ortega et al., 2018), COPD (Rabe et al., 2020) and NCFBE (Haworth et al., 2018; Aksamit et al., 2018), have chosen intervals including 7, 14 or 28 days.
- The Phase 2 study (INS1007-201) evaluated a similar population as that of the Phase 3 study (INS1007-301). In that study the mean total duration of Pulmonary Exacerbations (same definition as in Study INS1007-301) was 9.3 days. (Study INS1007-201 Clinical Study Report, 2020).
- A recent publication (Artaraz et al., 2020) evaluating a novel symptom diary for patients with NCFBE, the BEST diary (Bronchiectasis Exacerbation and Symptoms Tool), estimated the duration of Pulmonary Exacerbations is 15.3 days.

- A longer interval (28 days) decreases the apparent number of pulmonary exacerbations (for example, counting 2 discrete events as one), and artificially prolongs the duration of certain events.

FDA thanked the sponsor for providing justification for the proposed change in interval between pulmonary exacerbations as defined in the pivotal trial endpoints. FDA stated the change appeared reasonable for the ongoing phase 3 trial, provided that the data remains blinded and that exacerbations have been captured in a manner that allows an accurate count with the revised definition. Insmed confirmed they did not view the unblinded data and that individual exacerbations have been collected during the trial. Upon questioning from the FDA, the Sponsor claimed the initial use of 28 days to define the interval between exacerbations was chosen based on the precedent use in their phase 2 trial and other trials of NCFBE that had been conducted at the time. FDA further inquired whether Insmed re-analyzed their Phase 2 study data using the new, proposed interval between exacerbation events to which they reported affirmatively and concluded the amended definition resulted in an increase in the number of exacerbation events across both the treatment and placebo groups that did not impact the treatment effect. The sponsor stated they will submit the amended protocol and the Statistical Analysis Plan for FDA review.

With no further discussion, the meeting was concluded.

Question 13:

Does the Agency agree with the proposed strategy for providing safety data in the NDA?

FDA Response:

Your proposed clinical safety data package at the time of NDA submission includes information from 1682 adult participants and approximately 22 adolescent participants who have completed at least 52 weeks of treatment in Study INS1007-301 with 128 adult subjects in the follow up period and ongoing adolescent participants expected to have completed at least 29 weeks of treatment. You intend to provide additional data from subjects enrolled in study INS1007-201, the supportive Phase 2 study in subjects with NCFBE, multiple clinical pharmacology studies, and studies evaluating brensocatib for indications other than NCFBE. The proposed strategy for providing safety data appears sufficient to support filing, but the adequacy of the safety database will be a review issue.

Meeting Discussion:

No discussion occurred.

Question 14:

Does the Agency agree with the proposed strategy for providing safety data in the Day 120 Safety Update Report?

FDA Response:

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Your plan to submit additional safety information from the phase 3 pivotal trial, INS1007-301, the phase 2b study in subjects with CRSsNP, INS1007-221, and the ongoing expanded access program (EAP) gathered after the data lock for the initial NDA submission through 90 days prior to submission of the Day 120 safety update report appears reasonable.

Meeting Discussion:

No discussion occurred.

Question 15:

Does the Agency agree, assuming the unblinded data from Study INS1007-301 continue to support the safety profile, that no REMS is indicated?

FDA Response:

FDA makes decisions about requiring a REMS as part of a benefit-risk determination for a drug after an evaluation that includes integrated consideration of each of the statutory factors. Based on the limited information available, we have not identified a safety concern that appears to warrant a risk evaluation and mitigation strategy; however, a final determination will be made during the NDA review. We refer you to the guidance *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry*.⁸

Meeting Discussion:

No discussion occurred.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our DATE communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan **USE IF APPLICABLE FOR CONTROLLED SUBSTANCES:**, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the

⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rem-fdas-application-statutory-factors-determining-when-rems-necessary-guidance-industry>

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review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at [FDA.gov](https://www.fda.gov).⁹

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action. For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹⁰ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).¹¹

PRESCRIBING INFORMATION

⁹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

¹⁰ <https://www.fda.gov/media/86340/download>

¹¹ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹² and Pregnancy and Lactation Labeling Final Rule¹³ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

¹² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

¹³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.¹⁴

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹⁵

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				

¹⁴ <http://www.fda.gov/ectd>

¹⁵ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

(2)				
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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h¹⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*¹⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁸

SUBMISSIONS WITH REAL-WORLD EVIDENCE

¹⁶ <https://www.fda.gov/media/84223/download>

¹⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

¹⁸ <https://www.fda.gov/media/85061/download>

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.¹⁹ For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

See below

¹⁹ <https://www.fda.gov/media/124795/download>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JI HYUN LAROSE
01/18/2024 11:21:37 AM



133790

MEETING MINUTES

Insmmed Incorporated
700 US Highway 202/206
Bridgewater, NJ 08807-1704

Attention: Giselle Rose
Director, Regulatory Affairs

Dear Ms. Rose:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INS1007.

We also refer to the telecon between representatives of your firm and the FDA on July 8, 2020. The purpose of the meeting was to discuss the results of the Phase 2 study, the proposed Phase 3 study, and the overall adequacy of INS1007 program to support an NDA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-348-1896.

Sincerely,

{See appended electronic signature page}

Ngoc-Linh Do, PharmD
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 8, 2020; 2:00 – 3:00 PM
Meeting Location: Teleconference

Application Number: 133790
Product Name: INS1007

Indication: Treatment of Non-Cystic Fibrosis Bronchiectasis
Sponsor Name: Insmed Incorporated

Regulatory Pathway: 505(b)(1)

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Ngoc-Linh Do, PharmD

FDA ATTENDEES

Sally Seymour, MD, Director, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Banu Karimi-Shah, MD, Deputy Director, DPACC
Stacy Chin, MD, Clinical Team Leader, DPACC
Katherine Clarridge, MD, Clinical Reviewer, DPACC
Yongman Kim, PhD, Biostatistics Team Leader, Division of Biometrics III (DBIII), Office of Biostatistics (OB)
Dong-Hyun Ahn, PhD, Biostatistics Reviewer, Division of Biometrics III, OB
Lei He, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Ngoc-Linh Do, PharmD, Regulatory Project Manager, DPACC

SPONSOR ATTENDEES

Carlos Fernandez, MD, MBA, Senior Director, Clinical Development
Diane Fiorenza, BS, RAC, Vice President, Regulatory Affairs
Martina Flammer, MD, MBA, Chief Medical Officer
Kevin Mange, MD, MSCE, Senior Vice President, Clinical Development
Giselle Rose, Director, Regulatory Affairs
Andy Stautberg, General Manager, Pipeline Programs
Gene Sullivan, MD, FCCP, Chief Product Strategy Officer
Shande Tang, PhD, Director, Biostatistics
Ariel Teper, MD, Vice President, Clinical Development
Fang Xie, PhD, Vice President, Biometrics

1.0 BACKGROUND

On April 15, 2020, Insmmed submitted an End-of-Phase 2 meeting request to discuss the proposed Phase 3 study and the overall adequacy of INS1007 program to support an NDA submission. The proposed indication is for the treatment of adult patients with non-cystic fibrosis bronchiectasis (NCFBE).

The Division sent Preliminary Comments to Insmmed on July 1, 2020 and on July 6, 2020 the sponsor requested to focus the teleconference on questions 1 and 3 (part 1).

The questions from the briefing package, received on May 13, 2020, and FDA responses are in normal font, followed by the meeting discussion in **bold**.

2.0 DISCUSSION

Question 1

Does the Agency agree that a single Phase 3 study as designed is adequate to support the efficacy and safety reviews for the proposed indication?

FDA Response

Typically, replicate evidence of efficacy is required to support approval of a drug; however, a single clinical trial which demonstrates a statistically robust, clinically meaningful effect may be acceptable. The size, duration, and design for your proposed phase 3 study appear adequate to meet your stated objectives provided the results are consistent with the data generated in your phase 2 supportive study.

The FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>) describes some settings where a single, properly designed and analyzed study may be sufficient to support a marketing application, in particular, when there is independent substantiation of effectiveness from related data or when evidence from the single study is both clinically and statistically very persuasive. Without additional independent supportive evidence provided by convincing proof of concept and/or dose-ranging studies, or an additional Phase 3 confirmatory trial, statistical evaluation of a single trial should control the type 1 error rate at a level comparable to that of two independent clinical trials (i.e., evaluated at the one-sided significance level of $.025 \times .025 = .000625$).

Discussion

Based on the Guidance for Industry Providing Clinical Evidence of effectiveness for Human Drug and Biological Product, Insmmed inquired if the Division would consider a single Phase 3 trial with the study-wide, two-sided type 1 error of 0.05 as adequate to support an NDA.

The Division encouraged the Sponsor to keep the current Phase 3 study powered for 0.01 level as originally proposed. Given that NCFBE is not a rare disease, our expectation for a single Phase 3 trial with a supportive Phase 2 trial data is to demonstrate statistical significance at a two-sided type 1 error of ≤ 0.01 in order to establish substantial evidence of effectiveness. The Sponsor expressed concern about the possibility of the Phase 3 trial results yielding a p-value between 0.05 and 0.01. In the event that this situation occurs, the Division stated that the efficacy results would be a review issue.

Question 2

Does the Agency agree with the dose selection of 10 mg and 25 mg for Phase 3?

FDA Response

Yes, we agree with the dose selection of 10mg and 25 mg for your phase 3 study.

Discussion

No further discussion needed.

Question 3

Does the Agency agree that the patient population for the study is appropriate to support the proposed indication?

FDA Response

We do not entirely agree that the patient population you have chosen to study will accurately reflect and support a broad indication of non-CF bronchiectasis. For a phase 3 trial, we recommend that the enrollment criteria be as inclusive as possible to provide sufficient data to inform the benefit/risk assessment. In that light, we have the following recommendations regarding your proposed eligibility criteria:

1. We note that you have excluded some etiologies of non-CF bronchiectasis (e.g., common variable immunodeficiency, ABPA, COPD). Although we recognize that some etiologies may have alternative treatment options resulting in varying background standard of care therapies, you will need to allow enrollment of a wider range of non-CF related etiologies of bronchiectasis if you intend to seek an indication for all non-CF bronchiectasis. As proposed, your eligibility criteria appear to be overly restrictive, such as requiring mucopurulent or purulent sputum color by the Murray color chart and a post-bronchodilator FEV₁ >30% and excluding patients with existing periodontal disease. To ensure that the results from your study are generalizable to the broader non-CF bronchiectasis patient population, we recommend considering the necessity of each criterion with the aim of evaluating a study population that is representative of the target patient population.
2. You plan to exclude subjects with eGFR < 30 mL/min/1.73² in the proposed Phase 3 study INS1007-301. We acknowledge that you excluded subjects with

eGFR < 45 mL/min/1.73² in the completed Phase 2 study INS1007-201 and population PK analysis showed that “*INS1007 PK exposure at steady-state was comparable in subjects with creatinine clearance values between 45 and 80 mL/min and subjects with normal renal function*”. However, since the elimination pathway of INS1007 and the impact of renal or hepatic impairment on INS1007 PK are still unclear, we recommend that you closely monitor patients with renal or hepatic impairment in the proposed Phase 3 study.

Discussion to item 1

Insmed provided their rationale for the selected patient population and the exclusion criteria. The sponsor relayed that the intent is to enroll a population that best represents non-CF bronchiectasis (NCFBE) in the context of a clinical study while preventing unnecessary patient study discontinuation and minimizing events that could complicate interpretation due to patients' baseline conditions.

Acknowledging the Sponsor's rationale, the Division expressed concern that the proposed enrollment criteria, which explicitly exclude some underlying etiologies of NCFBE, would not evaluate a study population that is reflective of the intended target patient population. The Division recommended that the sponsor reexamine the inclusion and exclusion criteria to be as inclusive as possible and consider alternative measures to ensure subject retention in the study, e.g., allowing enrollment of patients with stable underlying disease. In addition, the Division noted the proposed enrollment criteria exclude patients with preexisting periodontal disease. While there is a theoretical risk for new or worsening gingival and periodontal disease with INS1007, in the absence of a safety signal in the phase 2 study, this exclusion criterion does not appear necessary. The Division encouraged the Sponsor to limit exclusion criteria to whatever extent is possible so that the study population is representative of the general population of NCFBE patients.

Question 4

Does the Agency agree with the safety assessments (e.g. adverse event reporting plan) and monitoring plan (e.g. for Adverse Events of Special Interest) in the Phase 3 study?

FDA Response

Yes, your proposed safety assessments and monitoring plan, including AESIs of severe infection, hyperkeratosis, gingival or periodontal disorders, and neutropenia appear reasonable.

Discussion

No further discussion needed.

Question 5

Does the Agency agree that the proposed safety database is adequate to characterize the safety profile of INS1007 to support a marketing application for the proposed indication?

FDA Response

We agree that the size and scope of the proposed safety database appears adequate to characterize the safety profile of INS1007. However, you have not adequately characterized the elimination pathway of INS1007 and the impact of renal and hepatic impairment on PK (refer to FDA Response to Question 3). Therefore, you will need to incorporate sufficient frequency of safety assessments to closely monitor renal and liver function during the trial.

For adverse events of special interest, we recommend descriptive (i.e., no hypothesis testing or margin selection), but prospectively planned analysis to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, or rate ratio, along with a confidence interval for the metric used for comparison).

Discussion

No further discussion needed.

Question 6

Does the Agency agree with the proposed study sample size, planned interim analysis, and sample size reassessment procedure?

FDA Response

Yes, your proposed study sample size, planned interim analysis, and sample size reassessment procedure appear to be reasonable. However, maintaining confidentiality to interim results is important to prevent operational bias. Clarify if and how the investigators and the study team will remain blinded to comparative interim data. If you proceed with such an interim analysis, there should be detailed documentation of any unblinding of interim results, the decision recommended by the Data Monitoring Committee (DMC), and minutes from all meeting (e.g., both closed and open DMC meeting minutes), and this documentation should be submitted in a potential future marketing application. We note that you plan to have an independent DMC review the interim data and that a DMC charter will be prepared. It would be helpful to submit the DMC charter along with the additional requested details on the proposed interim analysis for FDA review.

Discussion

No further discussion needed.

Question 7

Does the Agency agree that the Andersen-Gill model of analyzing recurrent events is an appropriate primary method for evaluating the planned primary endpoint in the Phase 3 study?

FDA Response

We acknowledge that the Anderson-Gill model could be sensitive using the inter-event time information in the analysis. However, we consider a negative binomial model to estimate ratio of exacerbation rates between groups as a model generating clinically readily interpretable results. You may provide a stronger justification for using the Anderson-Gill model over the negative binomial model. You may consider an analysis based on the negative binomial model as a primary analysis and the Anderson-Gill model as a supportive analysis.

Discussion

No further discussion needed.

Question 8

Does the Agency agree with the proposed statistical hypothesis testing procedures for controlling study-wise type I error rate?

FDA Response

Your proposed statistical hypothesis testing procedures for controlling study-wise type I error rate appears reasonable. However, according to your plan, to test the secondary endpoints in the hierarchy, you need to reject both hypotheses on the primary endpoint comparisons between two doses vs placebo. Note that with the current plan, you cannot proceed to test secondary endpoints for a dose with statistical significance on the primary endpoint when the other dose failed.

Discussion

No further discussion needed.

Question 9

Does the Agency agree that the overall Clinical Pharmacology program is adequate to support NDA submission?

FDA Response

We do not agree that the current clinical pharmacology program is adequate to support an NDA submission, we have the following recommendations:

1. Characterize the elimination pathway of INS1007 and address the impact of impaired renal or hepatic function on systemic exposure of INS1007. Refer to the FDA Guidance for Industry entitled “ *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)*”

(<https://www.fda.gov/media/78573/download>) and “*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (May 2003)*” (<https://www.fda.gov/media/71311/download>) for additional information.

2. You claim that *in vitro* studies indicated a low risk of drug-drug interactions caused by INS1007, involving CYPs and transporters. However, per Table 1 of the Meeting Background Material, whether INS1007 is a substrate of BCRP and other hepatic or renal transporters has not been evaluated. In the NDA submission, provide relevant information based on *in vitro* studies to determine the need for clinical drug interaction studies as recommended in the FDA Guidance for Industry entitled “*In Vitro Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020)*” (<https://www.fda.gov/media/134582/download>). The final determination of the adequacy will be a review issue.
3. We note that different formulations of INS1007 were used in the clinical development program. We recommend that you use the to-be-marketed (TBM) drug product in the critical clinical studies to avoid the need of formulation bridging. In addition, in your NDA submission, provide justification and/or clinical bridging data if you intend to borrow findings from previously conducted clinical studies that utilized a formulation different from the TBM drug product to support the prescribing information for INS1007.
4. We do not agree that the submitted information is adequate for the characterization of QT prolongation effects of your drug. To use the proposed clinical study (Study # INS1007-101) as a substitute for a thorough QT study as per ICH E14 Q&A (R3) 5.1, you will need to show that the PK and ECG data are collected at sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic exposures) such that a separate positive control would not be necessary (see ICH E14 Section 2.2.2).

In the absence of required exposure margin as described in ICH E14 Q&A (R3) 5.1, we recommend that you consider conducting a thorough QT study to satisfy E14. The thorough QT study can be designed using concentration-QTc analysis as the primary analysis. When submitting the thorough QT study protocol, include the following together with the protocol:

- a. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (<https://www.fda.gov/media/129685/download>)
- b. Statistical analysis plan
- c. Investigator’s Brochure

Discussion**No further discussion needed.****Additional Statistical Comments**

In determining your study design and statistical analyses, we recommend that you first consider the estimand of interest for your primary and key secondary endpoints. The recently finalized ICH E9(R1) addendum defines estimands. Each estimand should be described in sufficient detail. Specifically, the following five attributes should be specified for each estimand: (1) treatment regimens for patients to be evaluated (e.g., INS1007 10 mg, INS1007 25 mg, placebo); (2) populations of patients targeted by the clinical question (e.g., patients meeting inclusion/exclusion criteria, grouped according to randomized treatment assignment); (3) patient-level outcome to be measured (e.g., frequency of pulmonary exacerbation over the 52-week treatment period); (4) how intercurrent events will be handled (e.g., regardless of investigational product discontinuation or initiation of other treatments); and (5) population-level summary measure (e.g., between-group difference in the frequency of exacerbations over the 52-week treatment period). An estimand should describe the true clinical quantity you seek to target in your analyses. Ideally, these estimands should be adequately defined in both the protocol and the SAP.

Discussion**No further discussion needed.****3.0 ADDITIONAL INFORMATION****PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Peddsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.³

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁴ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁵

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to

⁵ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources⁶ and the CDER/CBER Position on Use of SI Units for Lab Tests website.⁷

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁷ <https://www.fda.gov/media/109533/download>

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the

⁸ <https://www.fda.gov/media/85061/download>

following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Attached are Insmed's submitted responses to questions 1 and 3 (part 1).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NGOC - LINH DO
07/27/2020 11:49:45 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	133790
Request Receipt Date	4/13/2020
Product	INS1007
Indication	For the treatment of adult patients with non-cystic fibrosis bronchiectasis (NCFB) for reducing exacerbations
Drug Class/Mechanism of Action	Small molecule inhibitor of the lysosomal cysteine protease dipeptidyl peptidase 1 (DPP1 or Cathepsin C)
Sponsor	Insmmed
ODE/Division	OII / DPACC
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	June 13, 2020

*Note: This document must be uploaded into CDER's electronic document archival system as a clinical review: **REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The proposed indication for INS1007 is for the treatment of adult patients with non-cystic fibrosis bronchiectasis (NCFB) for reducing exacerbations.

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

- Was the BTDR submitted to a PIND?**

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

- Consideration of Breakthrough Therapy Criteria:**

- a. Is the condition serious/life-threatening¹)? ☒YES ☐NO

If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Ragqio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Ragqio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

¹ For a definition of serious and life threatening see Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Deny Breakthrough Therapy Designation



Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Bronchiectasis is a persistent and sometimes progressive condition of the large bronchi characterized by abnormal dilation and destruction of bronchial walls. It is a heterogenous condition that can result from significant acute or chronic insult to the lungs. Cystic fibrosis (CF), caused by variants in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, is a well-characterized etiology of bronchiectasis and varies in prevalence depending on geographic region and population. In addition to CF, there are numerous and diverse disease processes that lead to bronchiectasis including acquired airway obstruction, immunodeficiencies, congenital anatomic defects of the airway, abnormal secretion clearance, and non-CF genetic defects, all of which are grouped within the umbrella classification of non-cystic fibrosis bronchiectasis (NCFB). Regardless of the etiology, which is often unidentified, the clinical manifestations of bronchiectasis include chronic cough, production of purulent sputum, recurrent pneumonias/exacerbations, hemoptysis, dyspnea, and activity limitation.

NCFB has been identified as an increasingly common disease in the US, with an estimated 110,000 individuals with a diagnosis of bronchiectasis in 2013.¹ While advances have been made in the treatment of CF by targeting the underlying genetic defect, there are very few causes of NCFB that respond to direct treatment and current therapy is aimed at controlling infection, reducing inflammation, and improving secretion clearance with concomitant bronchial hygiene. Frequent exacerbations in NCFB are the strongest predictor of future exacerbations and are associated with increased hospitalizations, reduced quality of life, and increased mortality. The Bronchiectasis Severity Index (BSI) was introduced to give more objective measures of mortality and morbidity in the NCFB population and consists of HRCT score, FEV1, Medical Research Council dyspnea score, bacterial colonization, prior hospital admission, and number of exacerbations. As an example, the one-year outcomes in the moderate severity group are a 0.9-4.8% mortality rate with a 1-7.2% hospitalization rate. The four-year outcomes in this group are a 4-11.3% mortality rate and a 9.9-19.4% hospitalization rate.²

While the underlying cause is often unidentified, the progressive airway destruction is thought to be secondary to the neutrophil-driven inflammation, including increased activity of neutrophil elastase,

increased viability of neutrophils, reduced phagocytosis, and increased release of myeloperoxidase.³ INS1007 is an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP1 or Cathepsin C), an enzyme that catalyzes the activation of granule serine peptidases in inflammatory cells, such as elastase and cathepsin G in neutrophils. INS1007 is hypothesized to decrease the damage from neutrophil-driven inflammation via decreased neutrophil elastase activity.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Phase 2 Study Endpoints

The primary efficacy endpoint was time to the first pulmonary exacerbation over the treatment period. Secondary efficacy endpoints included the rate of pulmonary exacerbations (number of events per person-time), change from screening in post-bronchodilator FEV1, and change from baseline in the Quality of Life Questionnaire-Bronchiectasis [QOL-B] respiratory symptoms score over the treatment period.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
 - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Pulmonary exacerbations are a clinically meaningful outcome for NCFB. While “time to first exacerbation” endpoints are acceptable for proof of concept studies and to provide supportive evidence of effectiveness, the Division prefers rate of exacerbations as a primary endpoint for confirmatory trials to support traditional approval of chronically administered products. Similarly, in a November 2017 meeting about NCFB, the Antimicrobial Drugs Advisory Committee (AMDAC) commented that time to first exacerbation may not be the best primary endpoint and that frequency of exacerbations is more clinically meaningful.

Improvement in pulmonary function tests (PFTs) such as FEV1 or FVC has been used as a surrogate endpoint to support traditional approval for some products used to treat other respiratory diseases, but the natural history of pulmonary function in NCFB and its relationship to outcomes such as risk of exacerbations, hospitalization, or death have not been well-characterized. Therefore, an improvement in

pulmonary function tests alone would have uncertain clinical significance in NCFB, and would likely be insufficient to support approval.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

There are currently no biomarkers the Division would consider likely to predict a clinical benefit for the proposed indication.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Currently, there are no approved therapies for prevention or management of NCFB exacerbations. Bronchiectasis is a heterogeneous condition and treatment of the underlying disease is often not possible, as the bronchiectasis is a manifestation of scarring that resulted from a prior injury or infection (e.g., severe pneumonia) or a result of an ongoing problem with secretion clearance that does not have a specific treatment (eg, primary ciliary dysfunction). Therefore, many types of medications are used to treat various aspects of the disease. For example, antibiotics, either oral or inhaled, are used to treat/suppress infection, bronchodilators and inhaled corticosteroids are used to treat any components of obstructive lung disease and inflammation, and mucolytic/expectorant therapies such as guaifenesin and acetylcysteine (Mucomyst) are used to help with the clearing/expectoration of excessive mucus.^{2,4-10} Studies of inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, colistin, and ciprofloxacin) for the prevention of NCFB exacerbations have yielded mixed results and many uncertainties remain regarding duration of treatment, frequency of administration, and appropriate endpoints for this use.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

(b) (4)

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.
- b. Include any additional relevant information. Consider the following in your response:
 - *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
 - *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
 - *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

The sponsor completed one study (INS1007-201) evaluating the safety, efficacy, pharmacodynamics, and pharmacokinetics of INS1007 in adults with NCFB in support of the BTDR as described in Table 1.

Table 1. Clinical Study Supporting the BDTR

Study ID	Trial Design	Treatment Groups	Population	Trial Endpoints
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⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

INS1007-201 Phase 2	R,DB, PC, PG, MC study	• INS1007 10mg • INS1007 25mg • Placebo Duration: 24 weeks N=256 (1:1:1)	• Adult NCFB • Diagnosis confirmed by CT • ≥ 2 exacerbations in past 12 months	• Primary: time to the first pulmonary exacerbation over 24 weeks • Secondary: rate of pulmonary exacerbations, change from screening in post-bronchodilator FEV1, and change from baseline in the QOL-B
R: randomized, DB: double-blind, PC: placebo-controlled, AC: Active control, MC: multicenter, QOL-B: Quality of Life Questionnaire-Bronchiectasis Source: Breakthrough Therapy Designation Request				

The trial was conducted at 16 sites across 14 countries. Subjects were excluded from the study if they had been on oral or inhaled antibiotics as chronic treatment for NCFB for < 6 months prior to the screening visit or taking cyclic doses of antibiotics. Randomization was stratified by prior macrolide use and the presence of *Pseudomonas aeruginosa* infection at baseline.

The mean age in the ITT population was 64.1 years, with a majority of subjects 65 years or older (58.6%). The majority of subjects were female (68.0%) and White (87.9%); the mean body mass index (BMI) was 25.91 kg/m². The percentage of subjects with 0 to 2 pulmonary exacerbations in the previous 12 months was 70.1%, 72.0%, and 58.6% in the placebo, INS1007 10 mg, and INS1007 25 mg groups, respectively. The mean score for the BSI at baseline was 8.5±4.55 and 8.4±4.33 in the INS1007 10 mg and 25 mg groups, respectively, compared with 7.9±4.30 in the placebo group, which corresponds to a moderate severity.

The study achieved its primary endpoint, prolonged time to first pulmonary exacerbation, for both strengths of INS1007 vs placebo. Forty-two subjects in the placebo group experienced an exacerbation compared to 26 subjects in the 10 mg group and 29 subjects in the 25 mg group. The median time to first exacerbation in the placebo group was 189 days, but there were not enough exacerbations in the INS1007 treatment groups to calculate median time as shown in Figure 1. One sided p-values for time to first exacerbation compared to placebo were p=0.014 and 0.022 for the 10 mg and 25 mg groups, respectively.

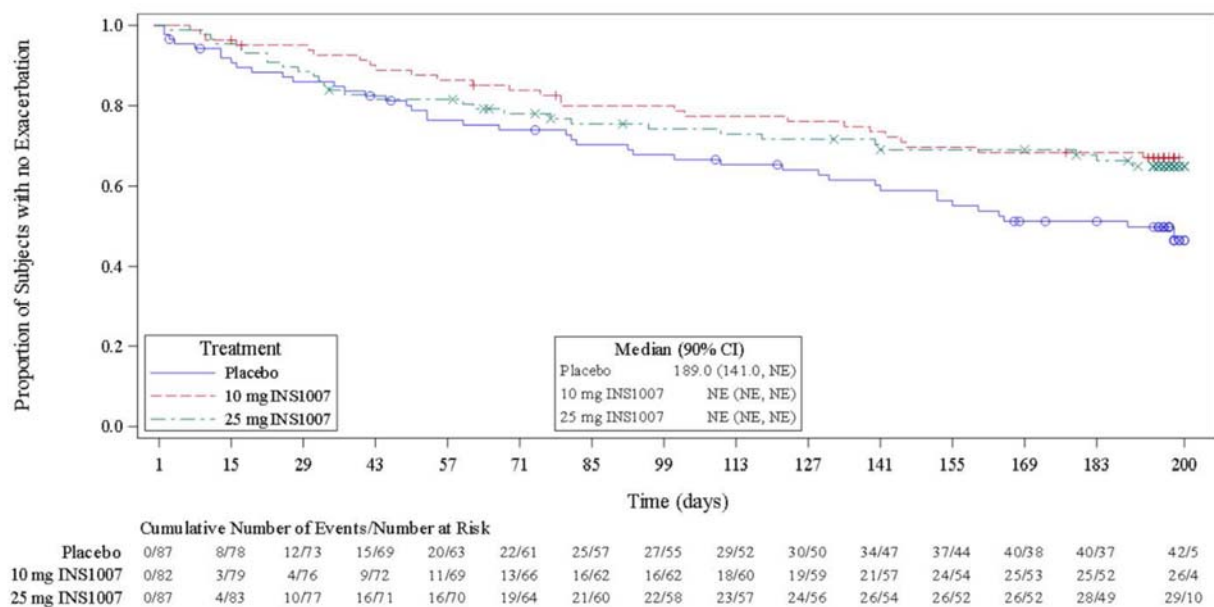


Figure 1. Kaplan-Meier Plot of Time to First Exacerbations. Source: Sponsor-submitted BTDR, p 8.

For the key secondary endpoint of rate of pulmonary exacerbations in number of events per person-time. The unadjusted rate of exacerbation events (80% CI) was 0.801 (0.572, 1.121) and 0.962 (0.711, 1.301) in the INS1007 10 mg and 25 mg groups, respectively, compared with 1.248 (0.956, 1.629) in the placebo group. The unadjusted annualized rate was statistically significantly lower in the INS1007 10 mg group than in the placebo group ($P=0.043$), but statistical significance was not achieved in the INS1007 25 mg group.

Adverse events have been relatively equally distributed across treatment groups. Headache was reported in >10% of subjects and increased with dose. Two subjects discontinued the study due to an adverse event of special interest. One in the placebo group developed pneumonia and one in the INS1007 25 mg group developed palmar erythema. There was one death during the study attributed to bronchiectasis progression in a 67-year-old female in the INS1007 25 mg treatment group.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

The Division recommends granting breakthrough therapy designation for oral INS1007 for the treatment of NCFB.

Currently, there are no approved therapies for the indication of NCFB. The data presented demonstrate preliminary evidence of substantial improvement on a clinically meaningful endpoint, time to first exacerbation, for patients in both the INS1007 10 mg and the INS1007 25 mg groups compared with

patients receiving placebo. The key secondary endpoint, rate of exacerbations, also trended in favor of treatment, with clinical significance met compared to placebo in the INS1007 10 mg group, but not the INS1007 25 mg group.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):
- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

The sponsor has requested and the Division has granted an end of phase 2 meeting to be held in July 2020 to review the results of INS1007-201 and to discuss the design of the proposed Phase 3 study entitled, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of INS1007 Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis" in support of an eventual NDA submission.

14. List references, if any:

- 1 Weycker, D., Hansen, G. L. & Seifer, F. D. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. *Chron Respir Dis* **14**, 377-384, doi:10.1177/1479972317709649 (2017).
- 2 Chalmers, J. D., Chang, A. B., Chotirmall, S. H., Dhar, R. & McShane, P. J. Bronchiectasis. *Nat Rev Dis Primers* **4**, 45, doi:10.1038/s41572-018-0042-3 (2018).
- 3 Bedi, P., Davidson, D. J., McHugh, B. J., Rossi, A. G. & Hill, A. T. Blood Neutrophils Are Reprogrammed in Bronchiectasis. *Am J Respir Crit Care Med* **198**, 880-890, doi:10.1164/rccm.201712-2423OC (2018).
- 4 Chalmers, J. D. *et al.* The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* **189**, 576-585, doi:10.1164/rccm.201309-1575OC (2014).
- 5 Chalmers, J. D. & Chotirmall, S. H. Bronchiectasis: new therapies and new perspectives. *Lancet Respir Med* **6**, 715-726, doi:10.1016/S2213-2600(18)30053-5 (2018).
- 6 Martinez-Garcia, M. A. *et al.* Spanish Guidelines on the Evaluation and Diagnosis of Bronchiectasis in Adults. *Arch Bronconeumol* **54**, 79-87, doi:10.1016/j.arbres.2017.07.015 (2018).
- 7 Martinez-Garcia, M. A. *et al.* Spanish Guidelines on Treatment of Bronchiectasis in Adults. *Arch Bronconeumol* **54**, 88-98, doi:10.1016/j.arbres.2017.07.016 (2018).

- 8 Pasteur, M. C., Bilton, D., Hill, A. T. & British Thoracic Society Bronchiectasis non, C. F. G. G. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* **65 Suppl 1**, i1-58, doi:10.1136/thx.2010.136119 (2010).
- 9 Polverino, E. *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* **50**, doi:10.1183/13993003.00629-2017 (2017).
- 10 Redondo, M. & Chalmers, J. D. Bronchiectasis Guidelines-Recommendations Into Practice. *Archivos de Bronconeumología (English Edition)* **55**, 286-288, doi:10.1016/j.arbr.2018.10.016 (2019).

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?
YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE E CLARRIDGE
06/02/2020 09:52:32 AM

STACY J CHIN
06/02/2020 10:01:59 AM

SALLY M SEYMOUR
06/02/2020 10:31:20 AM