CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217673Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217673
Product Name, Dosage Form, and Strength:	Brinsupri (brensocatib) tablets, 10 mg and 25 mg
Applicant Name:	Insmed Incorporated (Insmed)
FDA Received Date:	July 25, 2025
TTT ID #:	2024-12223-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

1 PURPOSE OF MEMORANDUM

Insmed Incorporated submitted revised container labels received on July 25, 2025 for Brinsupri. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels for Brinsupri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

As a part of the mid cycle communications with Insmed, the Agency requested Insmed provide updated prescribing information (PI) to incorporate the efficacy and safety information for both the 10 mg and 25 mg doses and efficacy and safety data. Thus, we note that the revised container labels submitted by Insmed include both 10 mg and 25 mg strengths.

3 CONCLUSION

Insmed Incorporated implemented all of our recommendations and we have no additional recommendations at this time.

[a] Owens, L. Label and Labeling Review for Brinsupri (NDA 217673). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAR 25. TTT ID: 2024-12223-1.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DAMON A BIRKEMEIER
07/29/2025 07:31:55 AM

The Clinical Inspection Summary

Date	July 9, 2025
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Elise Ferre, M.D., Clinical Reviewer, DPACC Elisabeth Boulos, M.D., Team Leader, DPACC Thomas Yung, PharmD, Regulatory Project Manager, DPACC Division of Pulmonology, Allergy, and Critical Care (DPACC)
NDA #	217673
Applicant	Insmed Inc.
Drug	Brinsupri (brensocatib)
NME (Yes/No)	Yes
Proposed Indication(s)	Treatment of non-cystic fibrosis bronchiectasis (NCFBE)
Consultation Request Date	January 22, 2025
Summary Goal Date	July 10, 2025
Action Goal Date	August 12, 2025
PDUFA Date	August 12, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bowler, Sigal, De Salvo, Cambursano, the contract research organization (CRO) (b) (4) and the sponsor Insmed Incorporated were inspected in support of NDA 217673, covering two studies: INS1007-201 and INS1007-301. Based on the results of the inspections, the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and the CRO and submitted by the sponsor appear acceptable in support of the respective indication. Of note, for Dr. Bowler, there was one unreported pulmonary exacerbation for one subject. While this omission does not affect the primary efficacy endpoint, as it was not the subject's first pulmonary exacerbation, it is relevant to the secondary endpoint of annualized rate of pulmonary exacerbations and is presented here for the review division's consideration.

II. BACKGROUND

According to the sponsor, Brinsupri (brensocatib), INS1007, is a small molecule inhibitor of the lysosomal cysteine protease dipeptidyl peptidase 1. The sponsor has submitted NDA 217673 for the treatment of non-cystic fibrosis bronchiectasis. Four BIMO Review Based clinical investigator inspections, a directed inspection of the CRO (b) (4) and a sponsor inspection were requested. The following describes studies INS1007-201 and INS1007-301:

Protocol INS1007-201: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks."

The study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation over the 24-week treatment period.

Sites: Subjects were randomized at 81 sites in Netherlands, Italy, Great Britain, Spain, Denmark, Belgium, Poland, Bulgaria, New Zealand, Australia, Singapore, Korea, and the United States.

Subjects: A total of 256 subjects were randomized (i.e., 87 subjects received placebo, 82 subjects received brensocatib 10 mg, 87 subjects received brensocatib 25 mg), and 225 subjects completed the Treatment Period (i.e., 74 subjects who received placebo, 76 subjects who received brensocatib 10 mg, 75 subjects who received brensocatib 25 mg).

Study initiation and completion dates: October 31, 2017 (date first subject enrolled); December 12, 2019 (date last subject completed the last visit)

Database lock date; study unblinding date: January 16, 2020; January 17, 2020

The study had a screening period that lasted up to six weeks. Subjects were randomized 1:1:1 to brensocatib 10 mg, brensocatib 25 mg, or matching placebo. During the treatment period, subjects were to receive study drug once a day for 24 weeks. Subjects were stratified by sputum culture positive for Pseudomonas aeruginosa status and maintenance antibiotic use. Subjects had an end of study visit at Week 28.

Key inclusion criteria: Male and female subjects, 18 to 85 years of age, with a clinical history of non-cystic fibrosis bronchiectasis (NCFBE) confirmed by chest computer tomography (CT) scan, body mass index >18.5 kg/m^2 at screening, current sputum producers with a history of chronic expectoration and able to provide a sputum sample at screening, sputum color at screening of mucoid purulent or purulent, and at least two documented pulmonary exacerbations in the past 12 months before screening. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Time to first pulmonary exacerbation over the 24-week treatment period.

Protocol INS1007-301: "A Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib in Participants With Non-Cystic Fibrosis Bronchiectasis (ASPEN)."

The study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the effect of brensocatib at 10 and 25 mg compared with placebo on the annualized rate of PEs.

Sites: Subjects were randomized at 365 sites in Europe, Middle East, Latin America, Asia, Australia, Canada, and the United States.

Subjects: A total of 1797 subjects were randomized (i.e., 579 subjects received placebo, 595 subjects received brensocatib 10 mg, and 593 subjects received brensocatib 25 mg), and 1381 subjects completed the Treatment Period (i.e., 457 subjects who received placebo, 458 subjects who received brensocatib 10 mg, 466 subjects who received brensocatib 25 mg).

Study initiation and completion dates: November 10, 2020 (date first subject enrolled); March 28, 2024 (date last subject completed the last visit)

Database lock date; study unblinding date: May 15, 2024; May 15, 2024

Subjects were randomized 1:1:1 ratio to receive placebo, brensocatib 10 mg daily, or brensocatib 25 mg daily for 52 weeks. The study was also designed to randomize approximately 40 adolescents ≥12 to <18 years of age in a 2:2:1 ratio to receive brensocatib 10 mg daily, brensocatib 25 mg daily, or matching placebo daily for 52 weeks. The study consisted of a six-week screening period, 52-week treatment period, and an end of study visit occurring 4 weeks after the end of the treatment. An Independent Clinical Endpoint Committee adjudicated all pulmonary exacerbations that occurred after randomization in a blinded manner to determine if the events fulfilled the protocol definition of a pulmonary exacerbation.

Key inclusion criteria: Male and female subjects, 12 to 85 years of age, with a clinical history consistent with NCFBE confirmed by chest CT scan. Subjects aged ≥18 years of age were required to a have at least two pulmonary exacerbations that required antibiotic prescription within 12 months before the screening visit, percent predicted post-bronchodilator FEV1 (ppFEV1) ≥30% and an absolute value ≥750 mL, mucopurulent or purulent sputum at the screening visit, and BMI ≥18.5 kg/m^2. Adolescents aged ≥12 to <18 years of age were required to have a at least one pulmonary exacerbation that required antibiotic prescription within 12 months before the screening visit, a post-bronchodilator FEV1 ≥30% of predicted normal value and an absolute value ≥ 750 mL, and body weight ≥30 kg. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Annualized rate of adjudicated pulmonary exacerbations.

III. RESULTS (by site):

1. Dr. Simon Bowler
Mater Misericordia Medical Centre
Brisbane
Australia
Protocol INS1007-201, Site AUS002
PDUFA Inspection Dates: February 17-21, 2025

For Protocol INS1007-201, 35 subjects were screened, 22 subjects were enrolled and randomized, and 16 subjects completed the study. Subject AUS002-(b) (6), randomized to placebo, discontinued due to an adverse event of eosinophilic esophagitis. Subject AUS002-(b) (6), randomized to 25 mg brensocatib, discontinued due to an adverse event of headache. Subject AUS002-(b) (6) randomized to 25 mg brensocatib, discontinued due to an adverse event of increased sputum and bronchial secretion. Subject AUS002-(b) (6) randomized to 25 mg brensocatib, discontinued due to an adverse event of depression. Subject AUS002(b) (6) randomized to 10 mg brensocatib, discontinued due to an adverse event of anxiety. One subject withdrew from the study.

An audit of the study records was conducted for 19 randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, Institutional Review Board submission and approvals, subject selection criteria, informed consents, investigational device controls, adverse event reporting, signed Investigator Agreements, financial disclosure statements, sponsor monitoring activities, IP accountability, concomitant medications, subject e-diaries, case report forms, and paper source records for verification of primary efficacy endpoint.

For study INS1007-201, the pulmonary exacerbation data to determine the primary efficacy endpoint, time to first pulmonary exacerbation over the 24-week treatment period, were entered by investigational staff into the sponsor's electronic data capture system, and no additional adjudication was conducted. The primary efficacy endpoint was verified by comparing the start dates reported for each pulmonary exacerbation in the paper source documents with the sponsor's data line listings.

An unreported pulmonary exacerbation occurred for Subject #AUS002-(b) (6) who was randomized to receive 10 mg of brensocatib. The subject exhibited four out of six symptoms defined in the protocol as indicative of a pulmonary exacerbation: increased cough, increased sputum volume, increased sputum purulence, and fatigue. These symptoms were documented from (b) (6), followed by antibiotic treatment from (b) (6). According to the protocol's definition, this event should have been classified as the subject's second pulmonary exacerbation. However, this incident was not recorded in the electronic data capture (EDC) system by the site nor included in the sponsor's subject data line listings.

Reviewer's comment: Per the source documentation and the sponsor's data line listings, Subject AUS002-(b) (6) had their initial pulmonary exacerbation from (b) (6), to (b) (6) (b) (6) The subject had a second pulmonary exacerbation which was not recorded in the EDC.

The site agreed that this second pulmonary exacerbation should have been reported in the EDC. While this omission does not affect the primary efficacy endpoint, as it was not the subject's first pulmonary exacerbation, it is relevant to the secondary endpoint of annualized rate of pulmonary exacerbations and is presented here for the review division's consideration.

There was one unreported adverse event. Subject AUS002-(b) (6) who was assigned to the placebo group, experienced a fifth toe fracture on their left foot on (b) (6). While this event was documented in the site's adverse event log, it was not transferred to the electronic data capture system. The site acknowledged that they failed to report this incident.

Reviewer's comment: This adverse event is unlikely to be caused by the investigational product but is presented here for the review division's consideration.

2. **Dr. Barry Sigal**
   Southeastern Research Center
   2932 Lyndhurst Avenue
   Winston Salem, NC 27103-4027
   Protocol INS1007-201**,** Site USA037
   PDUFA Inspection Dates: March 24-26, 2025

For Protocol INS1007-201, 21 subjects were screened, 12 subjects were enrolled and randomized, and nine subjects completed the study. Three subjects withdrew from the study.

An audit of the study records was conducted for all 12 randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, informed consent forms, Institutional Review Board correspondence and approvals, investigational product accountability and storage, concomitant medications, regulatory documentation, financial disclosures, eligibility checklists, adverse event reporting, and paper source records for verification of primary efficacy endpoint.

The event start date for the first pulmonary exacerbation during the 24-week treatment period was verified by comparing the data in the sponsor's data line listings with the site's paper source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

3. **Dr. Maria De Salvo**
   Centro Medico Dra De Salvo
   Pisos 1a, 6, 7
   Ciudad Autonoma De Buenosaires
   Argentina
   Protocol INS1007-301, Site ARG004
   PDUFA Inspection Dates: March 17-21, 2025

For Protocol INS1007-301, 65 subjects were screened, 49 subjects were enrolled and

randomized, and 43 subjects completed the study. Subject ARG004-(b) (6) randomized to 25mg brensocatib, withdrew due to an adverse event of generalized edema. Subjects ARG004-(b) (6) and ARG004-(b) (6) randomized to 25 mg brensocatib, died. Subject ARG004-(b) (6) randomized to placebo, died. Two subjects withdrew from the study.

Records of prior and concomitant medications were reviewed for 24 of 49 randomized subjects. Adverse event reporting was reviewed for 32 of 49 randomized subjects. Informed consent forms were reviewed for 12 of 49 randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, authority and administration, institutional ethics committee documentation, financial disclosures, subject records, investigational product accountability, monitoring activities, Clinical Studies Information Forms, protocol, financial disclosure statements, informed consent forms, and adverse event/serious adverse event reporting. There was no evidence of underreporting of adverse events. Since the primary efficacy endpoint was centrally adjudicated, it was not reviewed at the clinical investigator site. Refer to the section under CRO (b) (4) for the results of the primary efficacy endpoint data verification.

4. **Dr. Victor Cambursano**
   Instituto De Medicina Respiratoria
   Avenida Colon 2057
   Cordoba, X5003DCCE
   Argentina
   Protocol INS1007-301, Site #ARG005
   PDUFA Inspection Dates: March 25-28, 2025

For Protocol INS1007-301, 20 subjects were screened, 18 subjects were enrolled and randomized, and 16 subjects completed the study. One subject was lost to follow-up and one subject withdrew from the study.

An audit of the study records was conducted for eight of the 18 randomized subjects (i.e. Subjects (b) (6)). Records reviewed included, but were not limited to, protocol and amendments, subject records, financial disclosure statements, institutional ethics committee approvals, informed consent forms, adverse event reporting, clinical source data, investigational product accountability, concomitant medications, scales, laboratory collections, monitoring activities, and eligibility checklists. There was no evidence of underreporting of adverse events. Since the primary efficacy endpoint was centrally adjudicated, it was not reviewed at the clinical investigator site. Refer to the section under CRO (b) (4) for the results of the primary efficacy endpoint data verification.

5. (b) (4)

PDUFA Inspection Dates: (b) (4)

This inspection was a directed inspection that covered the verification of the primary efficacy endpoint, annualized rate of adjudicated pulmonary exacerbations, for Protocol INS1007-301's. For study INS1007-301, a Clinical Endpoint Committee (CEC) consisting of three independent physicians evaluated all reported pulmonary exacerbation events and determined whether these events met the protocol definition. The entire adjudication process, including review, assessment, and documentation, was conducted electronically within the Electronic Adjudication System (EAS) database. No physical records existed, as all dossiers and outcomes were processed and stored digitally in the EAS and managed by the CRO, (b) (4)

Source documents pertaining to the primary efficacy endpoint were reviewed for 33 subjects from Dr. Maria C. De Salvo (Site ARG004) and 14 subjects from Dr. Víctor H. Cambursano (Site ARG005) sites. As requested by the review division, the following title headings from the sponsor's subject data line listings were verified by comparing the data in the sponsor's data line listings with the site's electronic source documents:

- Start Date/End Date of the Pulmonary Exacerbation Event
- Clinical Endpoint Committee (CEC) Assessed Start and End Dates
- CEC Adjudicated Results

No discrepancies were noted. All events were confirmed to meet the protocol-defined criteria for pulmonary exacerbation.

6. Insmed Incorporated
700 US Highway 202/206
Bridgewater, NJ 08807-1704
PDUFA Inspection Dates: March 24-April 3, 2025

Documents reviewed included, but were not limited to, study protocols and amendments, organizational charts, standard operating procedures, various plans, monitoring visit reports, monitoring follow-up letters, oversight of vendors, selection and training of monitors, financial disclosure forms, trial master file, electronic data capture, protocol deviations, independent data monitoring meeting minutes, adverse event reporting, investigational product accountability records, and site monitoring records from four clinical investigator sites: Dr. Bowler (Site AUS002) and Dr. Sigal (Site USA037) under study INS1007-201 and Dr. De Salvo (Site ARG004) and Dr. Cambursano (Site ARG005) under study INS1007-301.

The sponsor terminated Site USA065 (Dr. Vinay Sikand) due to GCP non-compliance. The decision was based on several non-compliance issues at the site. Specifically, there was a lack of adequate principal investigator oversight, "troubling" communications from the site study

coordinator with representatives of the CRO, non-compliance with data collection as set forth in Section 11 of the Protocol, and non-compliance with the protocol. These issues prevented the sponsor and the CRO from engaging in the site monitoring activity, and the site was terminated. The FDA was notified appropriately. There was no evidence of subject harm.

The inspection found the site monitoring and oversight by the sponsor to be adequate.
In general, the sponsor appeared to be in compliance with Good Clinical Practice and FDA regulations.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 10, 2025
To:	Thomas Yung, MSN, CRNP **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	**Marcia Williams, PhD** **Team Leader, Patient Labeling** **Division of Medical Policy Programs (DMPP)**
From:	Tisa Ellis, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI),
Drug Name (established name):	BRINSUPRI (brensocatib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 217673
Applicant:	Insmed Incorporated

1 INTRODUCTION

On December 12, 2024, Insmed Incorporated submitted for the Agency's review a 505(b)(1) Original New Drug Application (NDA) 217673 for BRINSUPRI (brensocatib) tablets, for oral use. The sponsor proposes the indication for the treatment of non-cystic fibrosis bronchiectasis (NCFBE) in adult and pediatric patients 12 years of age and older with the recommended dose of 25 mg orally with or without food. Brensocatib, a new molecular entity (NME) with a novel mechanism of action, is an oral, selective, competitive, and reversible inhibitor of dipeptidyl peptidase 1 (DPP1) developed under an investigational new drug (IND) application number 133790, under the Division of Pulmonology, Allergy, and Critical Care (DPACC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Critical Care (DPACC) on December 27, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRINSUPRI (brensocatib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft BRINSUPRI (brensocatib) PPI received on December 27, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 4, 2025.
- Draft BRINSUPRI (brensocatib) Prescribing Information (PI) received on December 27, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 4, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 10, 2025

To: Thomas Yung, Project Manager, DPACC

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for BRINSUPRI™ (brensocatib) tablets, for oral use

NDA: 217673

In response to DPACC's consult request dated December 27, 2024, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and container labeling for Brinsupri.

Labeling: OPDP has no comments on the proposed labeling based on the draft labeling received by electronic mail from DPACC on June 4, 2025.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Container Labeling: OPDP has reviewed the attached proposed container labeling received by electronic mail from DPACC on June 4, 2025, and we do not have any comments.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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Addendum to DPACC Consult to DDD regarding NDA 217673 (brensocatib)
Additional consultant comments are in red, below.

Questions for DDD Reviewer:

DPACC requests DDD's recommendations for the most appropriate labeling strategies, including:

1. **Recommendations for presentation (e.g., grouping of terms) of dermatologic findings in labeling that would be most informative to prescribers.**
   DDD Response: *See Appendix 1 for recommended groupings of the most common AEs.*

   Addendum: *The Applicant's pooled AE terms for "hyperkeratosis" (skin thickening, which may be caused by friction or genetics) are inappropriate. None of the pooled terms are consistent with hyperkeratosis. For example, "skin lesion" is nonspecific, but suggests a discrete entity. "Seborrheic keratosis" is a common, benign neoplasm in adults typically due to age. In addition, "exfoliative rash" may be better pooled with "rash" or "dry skin" (other AEs listed in the proposed table).*

   Recommended grouping of the terms in Appendix 1 are based on the consultant's knowledge of the general clinical appearance and pathophysiology of these entities. However, the grouping of terms and "counting" of incidences that are ultimately pooled requires detailed analysis of the AEs by the reviewing division, taking into consideration the clinical understanding of the mechanism of action of the drug, expected presentations of AEs, and the investigator's accuracy in diagnosing the AE. In addition, reviewing divisions differ on the minimum incidence percentage threshold in the treatment arm and percentage difference from placebo that warrant inclusion in the AE table in Section 6. Therefore, we defer the decision about which AEs and associated pooled terms to include in Section 6 to the reviewing division.

2. **Assessment of whether any dermatologic findings warrant inclusion as a warning and precaution in Section 5.**
   DDD Response: *None.*

   Addendum: *Per the Guidance for Industry* ***Warnings and Precautions…****, Section 5 should "identify and describe a discrete set of adverse reactions and other potential safety hazards that are* ***serious*** *or* ***otherwise clinically significant*** *because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event…".*

   Of the AEs reported in the WILLOW and ASPEN studies, skin cancer (in DDD's opinion) are the only AEs that might meet this threshold. In general, skin cancer, typically due to extensive sun exposure, is common in adults, the subject population of these studies (ages 18-85, median age ~65 years). The incidence of skin cancers in any treatment arm of these studies (25mg brensocatib, 10mg brensocatib, or placebo) were low (<1%) and/or similar (<1% difference). Therefore, skin cancer doesn't warrant inclusion in Section 5.

In general, DDD does not recommend inclusion of relatively benign AEs in Section 5 such as "rash" if they are not serious (e.g., do not result in hospitalization or long-lasting sequelae), if the relationship of the AE and the use of the drug is unclear, and/or the overall incidence of the AE in the trials is fairly low. However, relatively benign AEs may be included if considered clinically significant. Because the determination of what is considered clinically significant must also take into account the seriousness of the disease being treated, the target population, the expected duration of drug use, and the alternative treatment options available to treat the condition, we defer to the reviewing division to decide what to include in this section.

3. **Identification and incorporation of any appropriate risk mitigation or management strategies to include in labeling.**
   DDD Response: *None.*

   Addendum: *Risk mitigation or management strategies may be warranted (typically in Section 2 or 5) if there are identifiable factors that, if known or controlled, may decrease the risk of serious adverse reaction (or its severity) related to the administration of the drug. We did not identify any risk mitigation or management strategies for this drug in the proposed subject population.*

Felisa S. Lewis, MD
Medical Officer
Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 25, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217673
Product Name, Dosage Form, and Strength:	Brinsupri (brensocatib) tablets, 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Insmed Incorporated (Insmed)
FDA Received Date:	December 12, 2024
TTT ID #:	2024-12223
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 INTRODUCTION

As part of the approval process for Brinsupri (brensocatib) tablets, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Brinsupri Prescribing Information (PI), Patient Package Insert (PPI), and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Brinsupri Prescribing Information (PI) and Patient Package Insert (PPI) and determined that they are acceptable from a medication error perspective.

However, the proposed Brinsupri container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Insmed Incorporated in Section 4.

4 RECOMMENDATIONS FOR INSMED INCORPORATED

Table 2. Identified Issues and Recommendations for Insmed Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The placement of the graphic at the end of the proprietary name competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name.	Placing a logo immediately before, within, or after the proprietary name can lead to misinterpretation because logos may look like an additional letter in the proprietary name or detract from legibility.	Delete, move, and/or decrease the prominence of the graphic at the end of the proprietary name.
2.	As currently presented, the “TM” symbol competes for	The prominence of the trademark symbol distracts from the readability of the	Decrease the prominence of the “TM” symbol and relocate

Table 2. Identified Issues and Recommendations for Insmed Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	prominence with the proprietary name and is located at the bottom right of the name.	proprietary name. Additionally, the symbol may be misinterpreted for a modifier.	it to the upper right area after the proprietary name.
3.	The linear barcode is oriented in a horizontal position.	Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode.	Ensure the scannability of the barcode. If it is not scannable, we recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.
4.	The "Keep out of reach of children" statement competes in prominence with critical product information (e.g., strength).	Critical product information such as the proprietary name and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15.	Consider moving the "Keep out of reach of children" statement to the side panel so it does not compete with the prominence of important product information on the principal display panel.
5.	The net quantity statement is in close proximity to the product strength.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing.	We recommend relocating the net quantity statement away from and ensuring it appears less prominent than the product strength, such as by relocating the net quantity statement to the bottom of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Brinsupri received on December 12, 2024 from Insmed Incorporated.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Brinsupri</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>brensocatib</td></tr>
<tr><td>Indication</td><td>the treatment of non-cystic fibrosis bronchiectasis in adult and pediatric patients 12 years of age and older</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>25 mg</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dose and Frequency</td><td>25 mg orally once daily</td></tr>
<tr><td>How Supplied</td><td>supplied as gray, round, film-coated tablets debossed with “25” on one side and “BRE” on the other in bottles of 30 tablets.
NDC 71558-002-30</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].</td></tr>
<tr><td>Container Closure</td><td>Table 1 Container Closure System
<table>
<tr><th>Tablet Strength</th><th>Tablet Count</th><th>Bottle Size</th><th>Closure Size</th><th>Liner/Material</th></tr>
<tr><td>25 mg</td><td>30</td><td>75 cc White Square HDPE</td><td>33 mm White (b) (4)</td><td>(b) (4)</td></tr>
</table></td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Brinsupri label and labeling submitted by Insmed Incorporated.

- Prescribing Information received on December 12, 2024, available from \\CDSESUB1\EVSPROD\nda217673\0001\m1\us\draft-annotated-uspi.pdf
- Patient Package Insert received on December 12, 2024, available from \\CDSESUB1\EVSPROD\nda217673\0001\m1\us\draft-clean-patient-information.pdf
- Container label received on December 12, 2024

B.2 Container Label

Container Label:

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C PRINGLE-OWENS
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DAMON A BIRKEMEIER
03/25/2025 07:56:38 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Immunology and Inflammation
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

M E M O R A N D U M

Date: February 7, 2025

From: Felisa Lewis, MD, Medical Officer, DDD

Through: Jill Lindstrom, MD, Division Director, DDD
Snezana Trajkovic, MD, Clinical Team Leader, DDD

To: Elise Ferré, PA-C, MPH, Medical Reviewer, DPACC
Elisabeth Boulos, MD, Clinical Team Leader, DPACC

CC: LCDR Susan Rhee, PharmD, BCSCP, Chief Project Management Staff, DDD

Re: Division of Dermatology and Dentistry Consult
Subject of consult: NDA 217673 (brensocatib)

Materials Evaluated:

- NDA 217673, SDN 1
  - Module 2.5 – Clinical Overview
  - Module 2.7.4 – Summary of Clinical Safety
  - Module 5.2 – Tabular Listing of All Clinical Studies
  - Module 5.3.5.3 – Integrated Summary of Safety
  - ISS ADAE and ADSL datasets
  - Proposed prescribing instructions (PI)

Consultation: The Division of Pulmonology, Allergy, and Critical Care (DPACC) consulted the Division of Dermatology and Dentistry (DDD) for an assessment of dermatologic adverse events (AEs) reported in clinical trials for Brinsupri (brensocatib), proposed for the indication of the treatment of non-cystic fibrosis bronchiectasis (NCFBE) in adult and pediatric patients 12 years of age and older. The proposed dosage is 25 mg PO once daily with or without food. This new drug application (NDA) has been submitted under NDA 217673, SDN 1.

Background: Brinsupri (brensocatib) is a new molecular entity (NME) developed under Investigational New Drug (IND) application number 133790. On June 5, 2020, the Agency granted Breakthrough Therapy Designation for brensocatib for the treatment of adult patients with NCFBE for reducing exacerbations. (b) (4)

(b) (4)

Brensocatib, proposed as a 25mg film-coated tablet, is an oral, selective, competitive, and reversible inhibitor of dipeptidyl peptidase 1 (DPP1, as known as Cathepsin C). DPP-1 inhibition is a novel mechanism of action (MOA), and there are no FDA-approved drugs with this MOA. The Applicant noted that a rare autosomal recessive condition, Papillon-Lefevre syndrome (PLS) that presents in children around the ages of 1-5 years, is caused by homozygous loss of function mutations of the cathepsin C gene, and its manifestations may be informative for the potential adverse event profile for brensocatib. More specifically, the manifestations of PLS are hyperkeratosis (e.g., diffuse palmoplantar keratoderma or focal psoriasiform plaques on elbows and knees), periodontitis and gingivitis leading to premature loss of deciduous and permanent teeth, and recurrent pyogenic skin infections.[1] Therefore, the Applicant defined the Adverse Events of Special Interests (AESIs) for this drug as hyperkeratosis, infection, and periodontal/gingival events.

Based on DPACC's initial safety analysis, pooled safety data from the phase 2 and phase 3 studies demonstrate a dose-dependent increase in these AESIs among the treatment groups, as well as other skin and subcutaneous tissue AEs, e.g., dermatitis, urticaria, and non-melanoma skin cancers. DPACC finds the Applicant's initial proposed labeling to be insufficient in the presentation of this safety signal. DPACC requests DDD's recommendations for the most appropriate labeling strategies.

The clinical development plan for brensocatib for the proposed indication of treatment of NCFBE consists of one phase 3, pivotal Study INS1007-301 (ASPEN) and a supportive phase 2 Study INS1007-201 (WILLOW). The safety database is comprised of a total of 1326 patients in the ASPEN and WILLOW studies with NCFBE who were treated with at least one dose of 10mg or 25mg brensocatib.

- INS1007-301 (ASPEN) – Phase 3 study of subjects 12 years and older with NCFBE that included 1156 subjects treated with brensocatib for 52 weeks.
  - 10 mg PO QD – 582 subjects (17 adolescents)
  - 25 mg PO QD – 574 subjects (16 adolescents)
  - Placebo – 563 subjects (8 adolescents)
- INS1007-201 (WILLOW) – Phase 2 study in of adult subjects with NCFBE that included 170 subjects treated with brensocatib for 24 weeks.
  - 10 mg PO QD – 81 subjects
  - 25 mg PO QD – 89 subjects

[1] Ahmad M, Hassan I, Masood Q. Papillon-lefevre syndrome. J Dermatol Case Rep. 2009 Dec 30;3(4):53-5. doi: 10.3315/jdcr.2009.1039. PMID: 21886733; PMCID: PMC3163345.

- Placebo – 85 subjects

In the proposed Prescribing Instructions, the Applicant discusses cutaneous AEs as described below in **Section 6.1** Clinical Trials Experience (excerpts related to dermatologic AEs):

(b) (4)

[redacted]

Consult Review:
For the purposes of this consult, my analysis was based on the ADSL and ADAE databases submitted to NDA 217673, SDN 1. Because brensocatib has a novel mechanism of action, the safety profile for this class of drugs has not been defined. For this consult, I included 1326 subjects with NCFBE in the ASPEN and WILLOW studies who received at least one dose of brensocatib at any dose level.

Conclusion/Recommendations:

- Review of the cutaneous treatment emergent adverse events (TEAEs) reported in the 1326 subjects in the ASPEN and WILLOW studies for the proposed indication of NBCFE reveals a number of cutaneous AEs that warrant consideration for inclusion in Section 6 of the proposed PI for brensocatib:
  - Rash
  - Dry skin
  - Eczema
  - Benign neoplasm
  - Skin cancer
  - Hyperkeratosis

  - Mouth ulceration
  - Bacterial infection
  - Stomatitis
  - Alopecia

  (See Appendix 1 for dictionary-derived terms pooled under each of the terms above.)
- One notable difference in the expected AE profile based on the PLS model and the reported AEs in the ASPEN and WILLOW trials is with respect to periodontal disease, which is a significant feature of PLS, leading to "premature loss of deciduous and permanent dentition at a very young age."[2] In the ASPEN and WILLOW trials, the incidence of periodontal disease in the brensocatib 25mg PO daily arm compared to the placebo was similar (1.2% vs 0.7% respectively). The trial period of 52 weeks may not be sufficient to reflect the periodontal disease progression and bone destruction/tooth loss that may occur with chronic use of this drug.

Questions for DDD Reviewer:

DPACC requests DDD's recommendations for the most appropriate labeling strategies, including:

1. **Recommendations for presentation (e.g., grouping of terms) of dermatologic findings in labeling that would be most informative to prescribers.**
   DDD Response: *See Appendix 1 for recommended groupings of the most common AEs.*

2. **Assessment of whether any dermatologic findings warrant inclusion as a warning and precaution in Section 5.**
   DDD Response: *None.*

3. **Identification and incorporation of any appropriate risk mitigation or management strategies to include in labeling.**
   DDD Response: *None.*

Felisa S. Lewis, MD
Medical Officer
Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Appendix 1. Recommended AE Groupings for Cutaneous AEs

[2] Sreeramulu B, Shyam ND, Ajay P, Suman P. Papillon-Lefèvre syndrome: clinical presentation and management options. Clin Cosmet Investig Dent. 2015 Jul 15;7:75-81. doi: 10.2147/CCIDE.S76080. PMID: 26203280; PMCID: PMC4507741.

APPENDIX 1. DDD Recommendations for Grouping of Cutaneous AEs

Primary dictionary-derived term (DDT) in **bold**, sub-bullets are recommended associated DDT terms. Terms with asterisks (*) are non-specific and verbatim terms/narratives assessed to confirm appropriate grouping. For example, the DDT of "hand dermatitis" may refer to chronic hand dermatitis versus palmoplantar keratoderma. Similarly, terms with crosses (†), such as facial and periorbital swelling, may be a manifestation of a hypersensitivity reaction and individual AEs should be assessed with verbatim terms/narratives to confirm appropriate grouping. Terms in italics may be considered for inclusion in the grouping.

Generalized conditions
Rash [inflammatory]
• Rash • Rash maculopapular • Rash pruritic • Rash papular • Rash erythematous • Rash exfoliative* • Dermatitis • Erythema • *Miliaria*
Dry skin
• Skin exfoliation • Xerosis • Skin fissures • Xeroderma • Cheilitis • Lip dry • Chapped lips
Eczema
• Dermatitis atopic • Eczema asteatotic • Hand dermatitis* • Dyshidrotic eczema • Eczema nummular • Eczema eyelids • Exfoliative rash • Keratosis pilaris • Superficial inflammatory dermatosis
Hyperkeratosis
• Palmoplantar keratoderma • Skin hypertrophy
Hypersensitivity

• Urticaria • Drug hypersensitivity • Urticarial dermatitis • Drug eruption • Toxic skin eruption • Adverse drug reaction • Swollen tongue† • Swelling of eyelid† • Swelling face† • Lip pruritus†
Skin cancer
• Basal cell carcinoma • Squamous cell carcinoma • Squamous cell carcinoma of skin • Bowen's disease • Malignant melanoma • Malignant melanoma in situ • *Anal squamous cell carcinoma*
Benign neoplasm
• Skin lesion • Skin papilloma • Seborrheic keratosis • Cyst • Dermal cyst • Benign neoplasm of skin • Lichenoid keratosis • Papule • Fibrous histiocytoma • Hemangioma • Lentigo • Skin mass • Eyelid cyst • Sweat gland tumor

Skin changes in sensation or appearance
Pruritus
• Ear pruritus • Vulvovaginal pruritus • Prurigo
Abnormal skin sensation
• Paresthesia • Burning sensation • Pain of skin

• Sensitive skin • Hypoesthesia • Hyperesthesia • Tenderness • Skin irritation

Infectious conditions
Serious infections
• Herpes zoster • Herpes zoster reactivation • Mycobacterium avium complex infection • Mycobacterial infection • Mycobacterium test positive • Pseudomonal infection • Pseudomonas test positive • Atypical mycobacterial infection
Bacterial infections
• Furuncle • Staphylococcal infection • Cellulitis • Subcutaneous abscess • Erysipelas • Abscess • Bacterial infection
Fungal/candidal infections
• Tinea capitis • Genital candidiasis • Fungal foot infection • Tinea pedis • Onychomycosis • Fungal skin infection • Candida infection • Angular cheilitis • Fungal infection • Genital infection fungal • Vulvovaginal candidiasis • Vulvovaginal mycotic infection
Viral infections
• Genital herpes simplex • VZV infection • Herpes simplex
Nonspecific infections

• Wound infection • Skin infection • Ear lobe infection

Hair changes
Alopecia
• Diffuse alopecia • *Hair growth abnormal* • *Hair texture abnormal*

Oral conditions
Gingival disorder
• Gingival pain • Gingival bleeding • Gingival swelling • Gingival discomfort • Gingival recession • Dental plaque • Gingivitis • Gingival injury
Periodontitis
• Periodontal disease • Tooth loss • Loose tooth • Tooth abscess
Toothache
• Pulpitis dental • Dental caries • Tooth infection • Dental discomfort
Mouth ulceration
• Palatal ulcer • Oral mucosa erosion • Tongue ulceration • Gingival ulceration • Aphthous ulcer
Stomatitis
• Mucosal hyperaemia • Oral pain • Oral discomfort • Mouth swelling • Paraesthesia oral • Oropharyngeal discomfort

• Hypoaesthesia oral • Oral mucosal erythema
Dry mouth
• Salivary gland cyst • Salivary gland disorder • Salivary gland enlargement • Benign salivary gland neoplasm
Oral candidiasis
• Oral herpes • Herpangina • Oral fungal infection • Oropharyngeal candidiasis

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/s/

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JILL A LINDSTROM
02/14/2025 12:13:44 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: January 24, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Thomas Yung, RPM
DPACC

Subject: QT Consult to NDA 217673 (SDN 1)

Note: Any text in the review with a light background should be inferred as copied from the Sponsor's document.

This memo responds to your consult to us dated 1/2/2025 regarding the Division's QT related question. We reviewed the following materials:

- Previous IRT reviews for IND 133790 dated 06/19/2020, 02/23/2022, 03/21/2022, 07/13/2022 and 02/21/2024 in DARRTS;
- Summary of clinical pharmacology studies (NDA217673 / SDN1);
- Clinical study report of Study INS1007-104 (NDA 217673 / SDN1); and
- Sponsor's proposed label (NDA 217673 / SDN1).

1 COMMENTS TO THE REVIEW DIVISION

Consult Request: The review division is asking for our review and comments on the sponsor's proposed labeling as it relates to QT findings from QT study report INS1007-104, entitled: A Two-part, Phase I, Double-blind, Placebo- and Positive-controlled Crossover Study to Investigate the Effects of Brensocatib on QT Interval in Healthy Subjects.

IRT's response: We previously reviewed the QT Study Report of INS1007-104 under IND 133790. The review includes the overall results of the Thorough QT study and concluded that brensocatib did not prolong the QTcF interval at the doses and exposures evaluated in INS1007-104 (120 mg SD; Cmax: 837 ng/mL).

The observed steady state geometric mean Cmax of 25 mg QD in patients with NCFBE (non-cystic fibrosis bronchiectasis) was 219 ng/mL in Study INS1007-201 (Day 29) (%CV: 62%)

while the steady state geometric mean Cmax of 40 mg QD in patients with congestive cardiac failure was 538 ng/mL. The final population PK model derived steady state geometric mean Cmax in adult patients participating in studies INS1007-201 and INS1007-301 were 254 ng/mL and 259 ng/mL respectively. The model derived Cmax in adolescents participating in study INS1007-301 was 419 ng/mL (Summary of clinical pharmacology, page 52 of 90). Therefore, the highest dose in the QTc assessment covers the steady state peak concentration in adolescents with NCFBE by approximately 2-fold.

Below are the proposed changes to the label submitted by the Applicant in SN001

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At concentrations approximately 2 (b) (4) times the steady state peak concentration of the maximum recommended daily dose of brensocatib in adult and adolescents with NCFB (b) (4), clinically significant (b) (4) QTc prolongation was not observed.

Reviewer's comment: We proposed (b) (4) (b) (4) (b) (4) *. We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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