Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217673
Priority or standard	Priority
Submit date(s)	12/12/2024
Received date(s)	12/12/2024
PDUFA goal date	8/12/2025
Division/office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review completion date	8/7/2025
Established/proper name	brensocatib
(Proposed) proprietary name	Brinsupri
Pharmacologic class	Dipeptidyl peptidase 1 (DPP1) inhibitor
Other product name(s)	brensocatib
Applicant	INSMED INC
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	25 mg once daily
Applicant-proposed indication(s)/ population(s)	Treatment of non-cystic fibrosis bronchiectasis in adult and pediatric patients 12 years of age and older
SNOMED CT code for proposed indication disease term(s)[1]	12295008 | Bronchiectasis (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	10 mg and 25 mg once daily
Approved indication(s)/ population(s) (if applicable)	Treatment of non-cystic fibrosis bronchiectasis in adult and pediatric patients 12 years of age and older
SNOMED CT code for approved indication disease term(s)[1]	12295008 | Bronchiectasis (disorder)

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AATD	alpha-1 antitrypsin deficiency
AE	adverse event
AESI	adverse event of special interest
AI	acceptable intake
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BE-CT	bronchiectasis-computed tomography
BEST	bronchiectasis exacerbation symptom tool
BID	twice daily
BMI	body mass index
BSI	bronchiectasis severity index
CatG	cathepsin G
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CT	computed tomography
CTSC	cathepsin C gene
CVID	common variable immunodeficiency
CYP	cytochrome P450
DDD	Division of Dermatology and Dental Products
DDI	drug-drug interaction
DILI	drug-induced liver injury
DPP1	dipeptidyl peptidase 1
EAT	enhanced Ames test
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels questionnaire
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FEF	forced expiratory flow
FVC	forced vital capacity
FMQ Broad	Broad Food and Drug Administration Medical Dictionary for Regulatory Activities query
GCP	good clinical practice
GD	gestation day
GEF	global evaluation factor
GLP	good laboratory practice
GQ	grouped query

HD	high dose
HLM	human liver microsomes
HP-β-CD	hydroxypropyl-β-cyclodextrin
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	investigational new drug
Ind_{C50}	half-maximal fold induction
Ind_{max}	maximal fold induction
IP	investigational product
iPSP	initial pediatric study plan
ITT	intent-to-treat
LLOQ	lower limit of quantification
LPS	lipopolysaccharide
LS	least squares
MAD	multiple ascending dose
MAR	missing at random
MoH	Ministry of Health
MRHD	maximum recommended human dose
NAG	N-acetyl-β-d-glucosaminidase
NCFB	non-cystic fibrosis bronchiectasis
NDA	new drug application
(b) (4)	(b) (4)
NE	neutrophil elatase
NOAEL	no observed adverse effect level
NSP	neutrophil serine protease
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamic
PEx	pulmonary exacerbation
PGIC	Patient Global Impression of Change scale
PGIS	Patient Global Impression of Severity scale
PI	prescribing information
PIND	pre-investigational new drug
PK	pharmacokinetic
PLD	phospholipidosis
PLS	Papillon-Lefèvre syndrome
PMR	postmarketing requirement
PP	per protocol
ppFEV1	percent predicted forced expiratory volume
PR3	proteinase 3
PRO	patient-reported outcome
PT	preferred term
QD	once daily
QOL-B	Quality of Life–Bronchiectasis
QOL-B RSS	Quality of Life–Bronchiectasis Respiratory Symptoms Domain Score
QOL-PCD	Quality of Life–Primary Ciliary Dyskinesia

QTcF	QT interval by Fridericia
SAD	single ascending dose
SAE	serious adverse event
SEE	substantial evidence of effectiveness
$T_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEM	transmission electron microscopy
T_{max}	time to maximum concentration
UA	usual activities
ULN	upper limit of normal
USP	United States Pharmacopeia
USPI	United States prescribing information
WBC	white blood cell

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

The Applicant, Insmed Incorporated, submitted an NDA for brensocatib, a first-in-class reversible inhibitor of dipeptidyl peptidase 1 (DPP1), for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in patients aged 12 years and older. The NDA was reviewed by a multidisciplinary team. Each team recommends approval for patients with NCFB aged 12 years and older.

To support the NDA for brensocatib, the Applicant submitted the results from two adequate and well-controlled clinical investigations: INS1007-301 (Study 301) and INS1007-201 (Study 201). Study 301 was a phase 3, randomized, double-blind, placebo-controlled trial that enrolled 1680 adults and 41 adolescents to evaluate brensocatib 10 mg and 25 mg administered once daily orally over 52 weeks. Study 201 was a phase 2, randomized, double-blind, placebo-controlled trial that enrolled 255 adults to evaluate brensocatib 10 mg and 25 mg administered once daily orally over 24 weeks. Study 301 demonstrated statistically significant improvements with both doses in the annualized rate of pulmonary exacerbations (PEx), time to first PEx, and responder status for exacerbation-free (i.e., responder analysis for proportion of subjects who were free from exacerbations). Results from Study 201 also demonstrated statistically significant improvements with both doses on the primary endpoint, time to first PEx.

The efficacy of brensocatib in adolescents aged 12 years and older is based both on efficacy and pharmacokinetic (PK) results in this population in Study 301 and on extrapolation from the adult populations in the pivotal trials, supported by similarities in NCFB across age groups. A postmarketing requirement (PMR) will be issued for an efficacy and safety study to evaluate brensocatib in children aged 6 to <12 years with NCFB.

The available safety database was adequate for review and demonstrated brensocatib is safe for its intended use. Risk mitigation for adverse effects will be addressed through communication in the United States prescribing information (USPI) and routine pharmacovigilance.

Based on the review team's benefit-risk assessment, both doses are recommended for marketing.

The action for this application is Approval.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

To support the proposed indication for brensocatib, the Applicant completed two adequate and well-controlled investigations, Studies 301 and 201. The trials demonstrated SEE for brensocatib 10 mg and 25 mg in 1,935 adult (Studies 301 and 201) and 41 adolescent (Study 301 only) subjects with NCFB. This review team's assessment of efficacy primarily leveraged data from Study 301 for several reasons. Study 301 incorporated more stringent Type I error control across key efficacy endpoints compared to Study 201, i.e., two-sided alpha of 1% for the primary endpoint and two-sided alpha of 5% for the key secondary endpoints. Although the primary endpoints for both trials are clinically meaningful—annualized rate of PEx in Study 301 and time to first PEx in Study 201—the annualized rate data provide more clinically relevant information for a chronic disease. Study 301 was also designed with a longer treatment duration (52 versus 24 weeks in Study 201), and brensocatib is intended for chronic use. Results from Study 301 demonstrated a statistically significant improvement in the primary endpoint, the annualized rate of PEx, in both brensocatib groups compared to placebo. Additional evidence of efficacy comes from the statistically significant improvements achieved among the key secondary endpoints in Study 301 and the primary endpoint of Study 201, time to first PEx. Additional supportive data come from the secondary endpoints of Study 201.

Substantial evidence of effectiveness in adolescents relies partially on results from Study 301, in which efficacy and PK results were comparable between adolescents and adults, and partially on extrapolation from the adult clinical development program, justified by similarities in NCFB across age groups.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• NCFB is a chronic, inflammatory lung disease characterized by a progressive cycle of airway destruction, impaired mucociliary clearance, bacterial airway colonization, and chronic infectious exacerbations that propagate further inflammation-induced tissue injury. • NCFB is a common disease with an estimated US prevalence between 230,000 and 430,000 cases with increasing incidence rates each year (Choate et al. 2021). • The underlying etiologies of NCFB are heterogenous with variable frequencies based on age. • Progession of NCFB leads to increased morbidity and loss of function, increased healthcare utilization and costs, and increased mortality (Henkle et al. 2018). For patients with NCFB in the US, all-cause mortality ranges from 11%-20% in the first 6 years following diagnosis (Feliciano et al. 2024). • There is substantial overalp in the pathophysiology, treatment, and progression of established NCFB between adults and children (including adolescents); however, there are differences in the frequencies of most common etiologies of NCFB and gaps in knowledge about the early inflammatory mechanisms leading to NCFB development in pediatric patients.	NCFB is a progressive respiratory condition with an increasing prevalence among adult and pediatric populations that results in morbidity and risk for early mortality. Although there is substantial similarity in the pathophysiology of NCFB between adult and pediatric populations, there are differences in the underlying etiologies and remaining uncertaintities about the early inflammatory mechanisms leading to NCFB development.
Current treatment options	• There are no approved therapies for NCFB. • Standard of care aims to address patients' symptoms and the sequelae of disease. Current standard of care includes: – Acute and/or chronic oral and inhaled antibiotics to treat and prevent exacerabtions; however, use increases the risk for developing antibiotic resistant organisms, thereby decreasing their effectivess in managing exacerbations over time.	There are no approved therapies for NCFB, and the current standard of care therapies target symptom management rather than the underlying cause(s) of NCFB inflammation. As a result, there is a high unmet medical need for a treatment that targets a common, inflammatory driver of NCFB pathology regardless of etiology.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Inhaled hypertonic saline, mucolytics, and physiotherapy to enhance airway mucociliary clearance. – Supplemental oxygen for those who are hypoxemic. – Less frequently, patients may be prescribed inhaled corticosteroids and bronchodialtors; however there is inconsistent evidence these therapies provide meaningful clinical benefit. • In cases of severe bronchiectasis and end-stage lung disease, patients may undergo lung resection or lung transplantation.	
Benefit	• Efficacy for brensocatib 10-mg and 25-mg doses in NCFB was established with two adequate and well-controlled trials: INS1007-301 (Study 301) and INS1007-201 (Study 201). • Study 301 demonstrated both brensocatib dose groups had a statistically signficant decrease in the primary endpoint of annualized rate of PEx compared to placebo, with minimal difference in the treatment effects between doses. • Study 301 also demonstrated both brensocatib groups met the key secondary endpoints of time to first PEx and responder status for being exacerbation-free with minimal to no difference in the magnitude of treatment effect between doses. • Study 301 demonstrated a statistically signfiicant increase in the key secondary endpoint of post-bronchodilator FEV1 in the 25-mg group only, although the difference in treatment effect compared to 10 mg was small (26 mL). • Study 201 demonstrated both brensocatib doses had a statistically significant increase in the primary endpoint, time to first PEx, consistent with and supportive of the results of Study 301. • The efficacy of brensocatib in 41 adolescent subjects was demonstrated in Study 301, in which adolescents demonstrated efficacy and pharmacokinetic responses in both brensocatib doses consistent with the overall population.	There is sufficient evidence to support that both brensocatib 10 mg and 25 mg result in statistically significant improvements for clinically meaningful endpoints: rate of PEx, time to first PEx, and resopnder status for being exacerbation-free. Study 301 demonstrated a statistically signfiicant increase in FEV1 with the 25-mg dose but not the 10 mg, but the size of the treatment effect for both doses was comparable. In addition, the treatment difference for the 25 mg vs placebo was too small to be clinically meaningful or justify exclusion of the 10 mg. Approval of the higher dose (vs the 10 mg only) is justified by the generally favorable safety profile observed (summarized below) and because the significant improvement in FEV1 observed with 25 mg suggests some patients may gain additional benefit from the 25-mg dose. Clinical benefit in adolescents aged 12 to <18 years is demonstrated by similar efficacy and PK responses to adults observed among adolescents in Study 301 and partial extrapolation supported by shared pathophysiological mechanisms of NCFB across age groups.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The safety program for brensocatib did not reveal major imbalances in deaths, SAEs, or AEs leading to treatment discontinuation with either dose compared to placebo. • Common AEs with increased incidence in the brensocatib groups in a dose-dependent manner include upper respiratory tract infections (including COVID-19), headache, rash, dry skin, and hyperkeratosis. • Other common AEs with increased incidence in the brensocatib groups compared to placebo, but not in a dose dependent pattern, include hypertension. • The safety review identified other, less common, dose-dependent AEs including alopecia and certain skin cancers. • Pre-defined AESIs based on the mechanism of action for brensocatib included hyperkeratosis, gingivitis/periodontitis, pneumonia, and serious infections. Hyperkeratosis was a common AE occurring in a dose dependent manner. The incidence of gingivitis/periodontitis was increased in the brensocatib groups in Study 201 but comparable to placebo in Study 301, possibly because of less robust monitoring in Study 301. The incidence of pneumonia was lower in the brensocatib groups, likely reflective of its treatment effect, as were serious infections. • The most frequent laboratory abnormalities included stable increases from baseline in AST and ALT, which resolved following treatment discontinuation. A greater increase was observed in the 25-mg group compared to the 10-mg group. There were no potential Hy's law cases and a few Temple's corollary cases equally distributed between both doses. • The safety profile in adolescents was consistent with the overall population.	The safety database was adequate for the comprehensive assessment of brensocatib for the proposed indication. The risks observed with brensocatib 10 mg and 25 mg do not outweigh the benefits for its intended use in patients with NCFB aged 12 years and older. The observed dose-dependent AEs provide additional support for marketing both brensocatib doses to provide patients with the option of a lower dose with comparable efficacy that may be better tolerated. Safety in adolescents was consistent with adults and partially extrapolated given the limited size of the adolescent safety database. Common and some rare but dose-dependent adverse reactions will be included in Section 6 of the USPI. Dermatologic and gingival/periodontal adverse reactions will be included as Warnings and Precautions in the USPI with actionable guidance for prescribers and patients. A REMS is not required at this time. Risk mitigation will be managed through labeling and routine pharmacovigilance.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; ALT, alanine aminotransferase; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; FEV1, forced expiratory volume in 1 second; NCFB, non-cystic fibrosis bronchiectasis; PEx, pulmonary exacerbation; PK, pharmacokinetic; SAE, serious adverse event; USPI, United States prescribing information

2.2. Conclusions Regarding Benefit-Risk

Non-cystic fibrosis bronchiectasis is a chronic, inflammatory lung disease characterized by a progressive cycle of airway destruction, impaired mucociliary clearance, and infectious exacerbations that propagate further inflammation-induced tissue injury. The prevalence of NCFB in the United States is estimated to be between 230,000 and 430,000 cases with an incidence increasing every year, attributable to an aging population and better recognition of the disease. There are no approved therapies indicated for NCFB. The current standard of care comprises treating and preventing pulmonary exacerbations with antibiotics and managing symptoms. Despite these therapies, NCFB remains a progressive disease leading to increased morbidity and early mortality. There is a significant unmet medical need for a therapy targeting the inflammatory response that drives the NCFB cycle. Brensocatib, a first-in-class, oral small molecule inhibitor of DPP1, will be the first treatment indicated for NCFB.

To support the NDA for brensocatib, the Applicant submitted results from two adequate and well-controlled investigations: Study 301 and Study 201. Both trials were randomized, double-blind, and placebo-controlled and evaluated the efficacy and safety of brensocatib 10-mg and 25-mg doses over 52 weeks (Study 301) and 24 weeks (Study 201). Study 301 demonstrated both brensocatib doses resulted in a statistically significant reduction in the annualized rate of PEx compared to placebo. Several clinically meaningful key secondary endpoints, including time to first PEx and responder status for being exacerbation-free, also demonstrated statistically significant improvements for brensocatib compared to placebo. In Study 201, both doses met the primary endpoint of time to first PEx, consistent with and supportive of the results in Study 301.

Across both trials, there were minimal to no differences in the magnitude of the observed treatment effects between the 10 mg and 25-mg doses. The Applicant initially proposed marketing only the 25-mg dose based on results for endpoints measuring lung function and a patient reported outcome, Quality of Life−Bronchiectasis Respiratory Symptom Domain Score (QOL-B RSS). In Study 301, the key secondary endpoint of change in post-bronchodilator forced expiratory volume in one second (post-BD FEV1) from baseline demonstrated a statistically significant improvement for the 25-mg dose but not the 10 mg; however, the magnitude of the effect was small, and additional analysis demonstrated the between-dose difference in effect size was even smaller. This review team found the magnitude of magnitude of the treatment effect for both doses to be comparable and not clinically meaningful; therefore, the statistical significance achieved for the 25-mg dose alone vs placebo was not persuasive enough to exclude the 10-mg dose as a treatment option. Refer to Section 6.3.1 for further discussion of this review issue.

Although the Agency considers the QOL-B RSS fit-for-purpose in the context of the brensocatib development program, results did not support a clinically meaningful improvement in the QOL-B RSS with either brensocatib dose. The lack of meaningful change in the QOL-B RSS was not an approvability issue since statistically significant improvements were achieved across multiple clinically meaningful endpoints. This conclusion did add further support to the comparable efficacy of both 10-mg and 25-mg doses. Refer to Section 6.3.1 and Section 6.3.3 for discussion of this review issue.

The safety database was adequate to support this review. The overall frequency of deaths was low (0.8% of the pooled safety database) and mostly secondary to complications of NCFB.

Treatment discontinuations attributable to adverse events (AEs) were infrequent and balanced across treatment arms. Adverse events of special interest were pre-defined based on mechanism of action and included hyperkeratosis, gingivitis/periodontitis, pneumonia, and severe infections (see Sections 7.2, 7.6.1.6, and 7.6.2.6). Only hyperkeratosis and gingivitis/periodontitis occurred at higher frequencies in the brensocatib groups compared to placebo. The most common AEs included upper respiratory tract infections such as Coronavirus disease 2019 (COVID-19), headache, hypertension, and skin-related events (rash, dry skin, and hyperkeratosis), among which upper respiratory tract infections, headache, and skin-related events demonstrated a dose-dependent relationship. Although drug-induced liver injury (DILI) was not observed in the clinical development program, there was a small dose-dependent increase from baseline in liver function tests (LFTs), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, while on treatment. Overall, the observed risks and toxicities can be adequately addressed through labeling and routine pharmacovigilance. The assessment of dose-dependent safety signals in the consideration of dose selection (Section 7.7.1) and skin-related adverse reactions (Section 7.7.2) were key safety issues in this review.

The data also support a favorable benefit-risk assessment for both doses of brensocatib in adolescents. Results from Study 301 demonstrated efficacy, safety, and PK results among the 41 adolescents that were comparable to the adult population. Partial extrapolation from the adult populations of Studies 301 and 201 is supported by similarities in the pathophysiology of NCFB across these age groups. This key review issue is discussed in Section 6.3.2 and Section 7.6.1.10.

The overall benefit-risk assessment supports approval of oral brensocatib 10 mg and 25 mg once daily for the treatment of NCFB in patients aged 12 years and older.

II. Interdisciplinary Assessment

3. Introduction

Non-cystic fibrosis bronchiectasis is a chronic respiratory condition of irreversible bronchial dilatation driven by pulmonary inflammation, mucus obstruction, recurrent infections, and progressive lung damage (Keir and Chalmers 2021; Chalmers et al. 2023). The lists of conditions known to cause or contribute to NCFB development is vast and heterogenous (Lonni et al. 2015). However, once NCFB is established, patients with bronchiectasis share a common, inflammatory cycle mediated by activated neutrophils that release neutrophil serine proteases (NSPs), such as neutrophil elastase (NE), which cause airway tissue injury leading to bronchial dilatation and eventual decline in lung function (Chalmers et al. 2023). Since NCFB results from inflammatory insults from a vast array of conditions and requires radiographic confirmation by computed tomography (CT) of the chest, patients may go unrecognized or receive a delayed diagnosis. Such delays in diagnosis affect epidemiological estimates of disease prevalence. Current estimates for US prevalence are between 230,000 and 430,000 cases (Choate et al. 2021) with up to 70,000 new cases per year (Weycker et al. 2017).

There are no approved therapies for NCFB. Management relies on identifying and treating the underlying cause, if possible, in combination with approaches to improve mucociliary clearance, treat and prevent respiratory infections, and address patient symptoms (McShane et al. 2013; Choi et al. 2024). Several factors complicate the treatment of infectious exacerbations, such as development of antimicrobial resistance and colonization of the airway with pathogenic bacteria and fungi (Aksamit et al. 2017; Maiz et al. 2018; Woo et al. 2019; Motta et al. 2024). Colonization with pathogenic microorganisms, particularly *Pseudomonas aeruginosa*, correlates with NCFB severity (Woo et al. 2019; Choate et al. 2021; Michaud and Thornton 2023); therefore, colonization status is an assessment category in the bronchiectasis severity index (BSI) (for further details see Section 15.1.3.1) (Chalmers et al. 2014). As a result, chronic macrolide administration is a prophylactic measure to reduce exacerbations caused by gram-positive and gram-negative bacteria, including *P. aeruginosa* (Serisier 2013; Gao et al. 2014; Wu et al. 2014; Fan et al. 2015). As NCFB progresses, patients with moderate or severe disease are more likely to develop serious exacerbations with opportunistic organisms, antimicrobial resistant organisms, or poly-microbial infections (Bonaiti et al. 2015; Maiz et al. 2016; Aksamit et al. 2017; Motta et al. 2024). For patients with severe, end-stage disease, surgical intervention, such as lung resection or transplant, may be offered.

Brensocatib is a first-in-class reversible inhibitor of DPP1, a papain-like cysteine peptidase expressed ubiquitously in human tissues with some of the highest levels identified in the lung and myeloid cells. DPP1 plays an important role early in neutrophil maturation during the promyelocyte phase, where it orchestrates activation and processing of NSPs (see Section 5). As a result, mature neutrophils exposed to brensocatib in their development will have few activated NSPs to secrete upon neutrophil activation (Chalmers et al. 2023). Through this inhibitory action on neutrophil function, brensocatib works to abrogate the NCFB inflammatory cycle and reduce further tissue injury.

DPP1 deficiency in humans, called Papillon-Lefèvre syndrome (PLS), is a rare condition caused by pathogenic variants in the cathepsin C gene (*CTSC*). The most common clinical features of PLS are severe oral inflammation and skin abnormalities leading to gingivitis, periodontitis, hyperkeratosis, and pyogenic skin infections. Less commonly, severe organ-specific infections and pneumonias have been reported (Section 7.2). Because brensocatib targets DPP1, these common and serious PLS features were pre-defined as adverse events of special interest and are reviewed in Sections 7.6.1.6 and 7.6.2.6. Skin-related adverse events are discussed in detail in Section 7.7.2.

Since there are no approved therapies for NCFB and the phase 2 data demonstrated a clinically meaningful and statistically significant improvement in the primary endpoint, brensocatib received breakthrough therapy designation on June 5, 2020, and was reviewed on a priority timeline.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Dose Selection

3.1.1.2. Efficacy in Adolescents

3.1.1.3. Quality of Life–Bronchiectasis Respiratory Symptoms Doman Score

3.1.2. Key Safety Review Issues

3.1.2.1. Dose Selection

3.1.2.2. Skin-Related Disorders

3.2. Approach to the Clinical Review

The Applicant submitted data from two clinical trials, Study 301 and Study 201, as the primary support for the safety and efficacy of brensocatib in NCFB. These trials were both international, multicenter, randomized, double-blind, placebo-controlled trials evaluating the efficacy and safety of brensocatib 10 mg and 25 mg over either 52 weeks (Study 301) or 24 weeks (Study 201). The design of the clinical development program is reasonable. The in-depth review of the clinical protocols is included in Section 15.

FDA biostatisticians performed efficacy analyses to confirm the data provided in support of the Applicant's primary and secondary efficacy endpoints, including expert review of the patient reported outcome measure performed by the Division of Clinical Outcomes Assessment and

patient-focused statistical support consultants. The efficacy review of brensocatib is in Section 6 and Section 16. The clinical reviewer and FDA clinical data scientist performed the safety review, located in Section 7 and Section 17. The clinical pharmacology team reviewed the clinical pharmacology data across the 11 submitted clinical studies and 5 reports for population PK analysis, exposure-response analysis, and physiologically-based pharmacokinetic (PBPK) analysis. The results of these analyses can be found in Sections 5.2, Section 6, and Section 14.

The approach to establishing SEE is reviewed in Section 3.3, and a summary of the clinical trials submitted by the Applicant in support of the efficacy and safety of brensocatib is reviewed below in Table 3.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

   The treatment of non-cystic fibrosis bronchiectasis in adult and pediatric patients 12 years of age and older.

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

   a. Adequate and well-controlled clinical investigation(s):

      i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence (May 1998; December 2019; September 2023a)

      OR

   c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch) (May 1998)

3. Complete response, if applicable

   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Brensocatib

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
INS1007-301 (Study 301, "APSEN") NCT04594369	Phase 3, R, DB, PC, PG, MC, MN study in subjects with NCFB >12 years of age	Control type: placebo Randomization: 1:1:1 for adults, 2:2:1 for adolescents Blinding: Double-blind	Drug: brensocatib Dosage: 10 or 25 mg QD Number treated: 1721 subjects including 41 adolescents Duration (quantity and units): 52 wk	Primary: Annualized rate of adjudicated PEx over the 52-week treatment period Secondary: - Time to first PEx - Responder status for exacerbation-free - Change in post-bronchodilator FEV1 at Week 52 - Annualized rate of severe PEs - Change in QOL-B Respiratory Symptoms Doman Score at Week 52 (adult participants only)	Number planned: 1660 subjects including 40 adolescents Number randomized and analyzed: 1721 subjects	402 centers in 36 countries (U.S. and ex-U.S.)

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
INS1007-201 (Study 201, "WILLOW") NCT03218917	Phase 2, NCFB subjects >18 years of age	Control type: placebo Randomization: 1:1:1 Blinding: Double-blind	Drug: brensocatib Dosage: 10 or 25 mg daily Number treated: 255 Duration (quantity and units): 24 wk	Primary: Time to first pulmonary exacerbation over the 24-week treatment period Secondary: - Annualized rate of PEx - Change in post-bronchodilator FEV1 - Change in QOL-B Respiratory Symptoms Domain Score - Change from Baseline in concentration of active NE in sputum	Number planned: 240 subjects Number randomized: 256 subjects	101 centers in 14 countries (U.S. and ex-U.S.)

Source: Clinical Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: DB, double-blind; FEV1, forced expiratory volume in 1 second; MC, multicenter; Mg, milligram; MN, multinational; N, number of subjects; NCFB, non-cystic fibrosis bronchiectasis; NCT, national clinical trial; NE, neutrophil elastase; PC, placebo-controlled; PE, pulmonary exacerbation; PG, parallel group; QD, once daily; QOL-B, quality of life questionnaire-bronchiectasis; R, randomized wk, week(s)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Sections 6.3.3 and 16.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	Section 2.1

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Brensocatib is a small molecule inhibitor of dipeptidyl peptidase 1 (DPP1, also known as cathepsin C). DPP1 activates NSPs including NE, proteinase 3 (PR3) and cathepsin G (CatG), during neutrophil differentiation in the bone marrow. Neutrophil accumulation in airways resulting in excess NSP activity can trigger structural damage in lung tissue, a central feature of bronchiectasis. Elevated NE activity in sputum in non-cystic fibrosis bronchiectasis (NFCB) is associated with decreased lung function. CatG is a proposed marker of chronic airway inflammation and PR3 activates proinflammatory markers, thereby contributing to NFCB disease progression. Therefore, the inhibition of DPP1, resulting in downstream attenuation of NSPs, is a reasonable therapeutic approach for NFCB. The submitted pharmacology studies suggest that

brensocatib effectively inhibits DPP1 and therefore reduces downstream activity of NSPs, resulting in a broad anti-inflammatory activity.

In in vitro studies, brensocatib inhibited DPP1 as a recombinant enzyme as well as in U937 cells. Furthermore, brensocatib inhibited DPP1 at similar potencies across various species including humans, dogs, rats, and mice. Brensocatib did not directly attenuate the activity of NSPs in enzyme assays. However, in in vivo models, brensocatib significantly reduced NE, PR3 and CatG activities in various mice and rat species including C57, BALB/c, Db/Db and NZBWF1/J mice, and Sprague Dawley and Wistar Han rats, confirming the role of DPP1 in this pathway. NSPs were inhibited to a similar extent in *CFTR* knockout mice, therefore indicating that the *CFTR* gene does not affect brensocatib activity. The time to pharmacologic activity showed maximum pharmacodynamic (PD) effect at 7 days post-dose in repeat dose studies and the inhibition of NSP activities plateaued beyond 7 days. DPP1 activity increased on day 1 post-dose but plateaued around day 7. The NSP activity recovered to baseline levels approximately 10 days after stopping dosing. Based on the in vitro inhibition of DPP1 but not NSPs, brensocatib was determined to be a "dipeptidyl peptidase (DPP1) inhibitor."

There are no established models for NCFB. Therefore, the Applicant has evaluated the activity of brensocatib in a lipopolysaccharide (LPS)-induced acute lung injury model. Brensocatib was orally administered for 8 days to Sprague Dawley rats, prior to intratracheal LPS challenge. NSP activity in blood, bronchoalveolar lavage (BAL) fluid, and bone marrow was variably reduced in the brensocatib-treated groups 24 hours post-LPS challenge. Brensocatib reduced TNFα levels with no effect on other cytokines or hydroxyproline levels. In an LPS-induced lung injury model in BALB/c mice, brensocatib was administered twice daily for 7 days prior to intranasal LPS challenge. At 2 and 5 days post-LPS challenge, NSP levels were reduced in the bone marrow of brensocatib-treated mice compared to vehicle or dexamethasone-treated mice. However, brensocatib treatment did not affect the other measures of acute lung injury including body and lung weights, cytokine levels, neutrophil levels in BAL fluid, and lowered respiratory capacity in animals. The totality of in vitro and in vivo pharmacology data submitted was considered sufficient to characterize the pharmacologic activity of brensocatib and supported the initiation of human clinical trials for the indication of NCFB.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	DPP1 inhibitor
Mechanism of action	Brensocatib is a small molecule inhibitor of DPP1. In vitro, brensocatib inhibits DPP1 enzymatic activity as recombinant enzyme as well as in intact U937 cells. In vivo, brensocatib inhibits DPP1 thereby reducing the activity of downstream effectors – NSPs including cathepsin G, proteinase 3 and neutrophil elastase. Elevated NSP activity in sputum in non-cystic fibrosis bronchiectasis is associated with decreased lung function and lung structural damage. Inhibition of DPP1 and downstream NSPs results in a broad anti-inflammatory activity.
Active moieties	Brensocatib is the active moiety.
QT prolongation	A thorough QT study (Study INS1007-104) was conducted. Brensocatib did not prolong the QTcF interval following a single oral dose administration of 120 mg brensocatib (4.8 times the highest recommended dose). Refer to IND133790 IRT-QT Study Review dated 02/21/2024 for more details.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td></td><td>General Information</td></tr>
<tr><td>Bioanalysis</td><td>Brensocatib concentrations in human plasma samples have been measured using adequately validated LC-MS/MS assays in clinical studies. All clinical samples were analyzed within the established stability period. Overall, the bioanalytical method validation and performance is acceptable.</td></tr>
<tr><td>Healthy subjects versus patients</td><td>Based on population PK analysis, brensocatib pharmacokinetics is similar in healthy subjects and patients with NCFB.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>Table 6. Geometric Mean (SD) Brensocatib Exposure at Steady-State Following 10 mg or 25 mg QD Based on Population PK Analysis
<table>
<tr><th rowspan="2">PK Parameter</th><th colspan="2">Dosing Regimen</th></tr>
<tr><th>10 mg QD</th><th>25 mg QD</th></tr>
<tr><td>AUC_{tau} (ng*h/mL)</td><td>1356 (590)</td><td>4065 (1757)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>85.4 (29.0)</td><td>259 (86.9)</td></tr>
<tr><td>C_{min} (ng/mL)</td><td>40.0 (21.8)</td><td>118 (64.6)</td></tr>
</table>
Source: Pharmacometrics Reviewer's analysis</td></tr>
<tr><td>Range of effective dose(s) or exposure</td><td>In the phase 2 dose ranging study (INS1007-201), two dosing regimens (i.e., 10 and 25 mg QD) were evaluated. Both doses produced a clinically significant difference in time to first PEx compared to placebo. Both doses were selected for further evaluation. In the phase 3 study (301), both 10 and 25 mg QD dosing significantly reduced the adjudicated annualized rate of PEs (primary efficacy endpoint) compared to placebo. See Section 6 for additional details on the efficacy assessment.</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>In healthy subjects (n=6), a single 120 mg oral dose of brensocatib was administered. At this dose, brensocatib C_{max} and AUC_{inf} were 1130 ng/mL and 17500 ng*h/mL, respectively (Study INS1007-104).</td></tr>
<tr><td>Dose proportionality</td><td>Brensocatib C_{max} and AUC increased slightly more than dose proportionally over the dose range of 10 to 40 mg. In healthy subjects (n=8/dose), following 10 to 40 mg QD dosing, brensocatib geometric mean steady state C_{max} and AUC_{tau} increased by 5.1- and 5.3- fold, respectively, for a 4-fold increase in dose (Study INS1007-101). In patients with NCFB, popPK-estimated brensocatib geometric mean steady state C_{max} and AUC_{tau} increased by 3-fold from 10 mg to 25 mg.</td></tr>
<tr><td>Accumulation</td><td>Following QD administration at 10- to 40-mg doses in healthy subjects, the accumulation ratio at steady state is approximately 1.5 based on C_{max} (range from 1.3 to 1.8) and 2 based on AUC_{tau} (range from 1.6 to 2.2) (Study INS1007-101). Following QD administration of 10 or 25 mg in subjects with NCFB, the accumulation ratio at steady state ranged from 2.3 to 3.8 for C_{max} and 3.0 to 4.7 for AUC_{0-8}.</td></tr>
<tr><td>Time to achieve steady-state</td><td>Based on C_{trough} in phase 2 and phase 3 studies, brensocatib steady state was reached within 4 weeks following QD dose administration.</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial/study formulations</td><td>Two oral tablet formulations, i.e., phase 2 tablet (manufactured by (b) (4)) and phase 3 tablet (manufactured by Patheon), were used in the phase 2 and phase 3 trials as well as most of phase 1 studies. The proposed to-be-marketed formulation (10 mg and 25 mg tablets) is identical to the phase 3 tablet formulation, except for differences in the tablet color and debossing of the core tablet. Comparison of dissolution profiles was conducted to bridge the phase 2, phase 3, and to-</td></tr>
</table>

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td></td><td>be-marketed drug products. Refer to Section 9 for the CMC and Biopharmaceutic reviews regarding the adequacy of formulation bridging.</td></tr>
<tr><td></td><td>Absorption</td></tr>
<tr><td>Bioavailability</td><td>The absolute oral bioavailability of brensocatib was not assessed in human. Based on data from the mass balance study (INS1007-103), following a single oral dose of 40 mg, the oral absorption of brensocatib in human is approximately 80% or higher.</td></tr>
<tr><td>T_{max}</td><td>Following a single dose oral administration of 10 mg or 25 mg brensocatib in healthy subjects, the median T_{max} of brensocatib was 1.0 hours (range: 1.0-2.0 hours) and 1.4 hours (range: 0.5-3.0 hours), respectively, under fasted conditions (Study INS1007-101).</td></tr>
<tr><td>Food effect (fed/fasted) Geometric least square mean and 90% CI</td><td>Brensocatib exposure (C_{max} and AUC) remained comparable when a single 40-mg dose was administered under fasted or fed (high-fat and high-calorie) conditions (Study INS1007-101).

Table 7. Summary of Food Effect on Brensocatib Exposure
<table>
<tr><th>PK Parameters</th><th>Geometric Least Square Mean Ratio, 90% CI</th></tr>
<tr><td>C_{max}</td><td>1.01 (0.81, 1.26)</td></tr>
<tr><td>AUC_{last}</td><td>1.01 (0.97, 1.06)</td></tr>
<tr><td>AUC_{inf}</td><td>1.00 (0.95, 1.05)</td></tr>
</table>
Source: Table 11-12 of Study INS1007-101 clinical study report

T_{max}: The median T_{max} was delayed from 1.3 hours (fasted) and to 2.0 (fed) hours.

Fed condition: a single 40-mg dose of brensocatib was administered approximately 30 minutes after the start of breakfast and within 5 minutes of the subject completing the high-fat and high-calorie breakfast, including 2 eggs, 2 strips of bacon, toast with butter, hashbrown and whole milk (total calorie count was 990 cal, fat content was 57 g (513 cal)).</td></tr>
<tr><td></td><td>Distribution</td></tr>
<tr><td>Volume of distribution</td><td>Following QD administration of 10 or 25 mg brensocatib to inpatients with NCFB, the estimated steady state volume of distribution of brensocatib ranged from 126 to 138 L.</td></tr>
<tr><td>Plasma protein binding</td><td>In human plasma, brensocatib is approximately 87.2% protein-bound.</td></tr>
<tr><td>Drug as substrate of transporters</td><td>Brensocatib is a substrate of P-gp and BCRP, but not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2.</td></tr>
</table>

Characteristic	Drug Information
	Elimination
Mass balance results	In the mass balance study INS1007-103, following a single oral dose of 40 mg of [14C]-brensocatib containing approximately 100µCi radioactivity, 82.5% of the administered radioactivity was recovered within 312 hours postdose, in which 54.2% (22.8% as unchanged form) was in urine and 28.3% (2.4% as unchanged form) was in feces. A total of 27 quantifiable metabolites were detected in plasma, urine, and feces, of which the structures of 9 metabolites were identified. Based on AUC_{last} in human plasma, unchanged brensocatib and thiocyanate (M8, the major circulating metabolite) accounted for 16.2% and 51% of the total radioactivity, respectively. All remaining metabolites accounted for <1% of total AUC_{last}. Aside from unchanged brensocatib, which was the most abundant component in urine, all other components were minor (<10% of dose) to trace (<1% of dose) in abundance. Thiocyanate (M8) was a minor urinary metabolite, accounting for a total of 1.62% of the dose. In feces, based on the pooled samples from 0 to 216 hours, metabolite M17 was the most abundant component, accounting for 3.8% of the radioactive dose. Brensocatib, M13, and M33 accounted for 2.4%, 1.3%, and 1.2% of the dose, respectively. All other metabolites were trace in abundance. Thiocyanate was not detected in feces.
Clearance	The apparent oral clearance of brensocatib ranged from 6.4 to 10.7 L/hour in healthy subjects (Studies INS1007-101, INS1007-102, INS1007-103, INS1007-105). Based on population PK analysis, the estimated apparent oral clearance of brensocatib in patients with NCFB ranged from 2.6 to 3.0 L/h.
Half-life	Following a single oral dose of brensocatib at 10 mg or 25 mg, the half-life of brensocatib ranged from 25 to 39 hours in healthy subjects (Studies INS1007-101, INS1007-102, INS1007-103, INS1007-105). Based on population PK analysis, the estimated half-life of brensocatib in patients with NCFB ranged from 33 to 40 hours.
Metabolic pathway(s)	Brensocatib is mainly metabolized by CYP3A4/5 (97%) and to a lesser extent, by CYP2C8 (2%) and CYP2D6 (1%). Based on the mass balance study (INS1007-103), brensocatib was metabolized primarily via oxidation, hydrolysis, oxidative dealkylation, sulfuration, and carbamoyl glucuronidation. Thiocyanate (M8) is the major circulating metabolite, accounting for 51% of the total radioactivity in human plasma. Note that thiocyanate (M8) is an endogenous molecule with GRAS status. Thiocyanate concentrations were measured in multiple studies, including the phase 2 study (INS1007-201) with the 25 mg QD dose in patients with NCFB and study INS1007-104 in healthy subjects with a 120 mg single dose. The baseline-corrected thiocyanate concentrations (range: −5.4 to 2.1 µg/mL) were generally low across studies.
Primary excretion pathways (% dose)	In the mass balance study (INS1007-103), following a single oral dose of 40 mg of [^{14}C]-brensocatib, 82.5% of the administered radioactivity was recovered within 312 hours postdose, in which 54.2% (22.8% as unchanged form) was excreted in urine and 28.3% (2.4% as unchanged form) was excreted in feces.

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Based on population PK analysis, there is no clinically significant effect of body weight on the pharmacokinetics of brensocatib. A dosage adjustment based on body weight is not recommended.
Age	Based on population PK analysis, there is no clinically significant effect of age on the pharmacokinetics of brensocatib. A dosage adjustment based on age is not recommended.
Renal impairment	Following a single oral administration of 25 mg brensocatib, brensocatib exposure (C_{max} and AUC) was comparable in subjects with mild renal impairment (eGFR: 60 to 89 mL/min/1.73m^2) compared to subjects with normal renal function. Brensocatib C_{max} and AUC increased by 10% and 27%, respectively, in subjects with moderate renal impairment (eGFR: 30 to 59 mL/min/1.73m^2), but decreased by 17% and 28%, respectively, in subjects with severe renal impairment (eGFR: 15 to 29 mL/min/1.73m^2) compared to subjects with normal renal function (Study INS1007-102). The observed changes in exposure are not considered clinically relevant, and no dosage adjustment is recommended.
Hepatic impairment	Following a single oral administration of 25 mg brensocatib, compared to subjects with normal hepatic function, brensocatib C_{max} and AUC increased by 12% and 20%, respectively, in subjects with mild hepatic impairment (Child-Pugh 5-6), remained comparable in subjects with moderate hepatic impairment (Child Pugh 7-9), and decreased by 26% and 20%, respectively, in subjects with severe hepatic impairment (Child-Pugh 10-15) (Study INS1007-105). The observed changes in exposure are not considered clinically relevant, and no dosage adjustment is recommended.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	At clinically relevant concentrations, brensocatib is not an inhibitor of CYPs 1A2, 2A6, 2C8, 2C9, 2C19, 2E1, 2B6, 2D6, 3A4/5. Brensocatib may be a weak CYP3A4 inducer, but not an inducer of CYPs 1A2, 2B6, 2C8, 2C9, or 2C19. Based on PBPK analysis, co-administration of brensocatib is unlikely to change midazolam (CYP3A4 substrate) exposure.
Inhibition/induction of transporter systems	At clinically relevant concentrations, brensocatib is not an inhibitor of P-gp, OAT1, OCT2, OAT3, or OATP1B3, and not expected to inhibit OATP1B1, MATE1, MATE2K, or BCRP.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Victim)
Impact of inhibitors of metabolism enzymes or transporters	Brensocatib is mainly metabolized by CYP3A4. Brensocatib is also a substrate of the transporters P-gp and BCRP. When co-administered with the strong CYP3A4 and P-gp inhibitor, clarithromycin, brensocatib C_{max} and AUC increased by 68% and 55%, respectively, relative to that after administration of brensocatib alone. When co-administered with the moderate CYP3A4 and P-gp inhibitor, verapamil, brensocatib C_{max} and AUC increased by 53% and 32%, respectively, relative to that after administration of brensocatib alone. No clinical DDI studies were conducted to evaluate the impact of BCRP inhibitors alone on brensocatib exposure. However, BCRP inhibitors are unlikely to have a clinically relevant impact on brensocatib pharmacokinetics. Refer to section 8 for more details.
Impact of inducers of metabolism enzymes	When co-administered with the strong CYP3A4 inducer rifampin, brensocatib C_{max} and AUC decreased by 15% and 33%, respectively, relative to that after administration of brensocatib alone.
Impact of proton-pump inhibitor	When co-administered with the proton-pump inhibitor esomeprazole, brensocatib C_{max} and AUC were unchanged compared to that after administration of brensocatib alone.

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum plasma concentration; CMC, chemistry, manufacturing, and controls; C_{min}, minimum plasma concentration; C_{trough}, trough concentration; CYP, cytochrome P450; DDI, drug-drug interaction; DPP1, dipeptidyl peptidase 1; eGFR, epidermal growth factor receptor; EPC, established pharmacologic class; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NCFB, non-cystic fibrosis bronchiectasis; NSP, neutrophil serine protease; PBPK, physiologically-based pharmacokinetic; PEx, pulmonary exacerbation; PK, pharmacokinetic; popPK, population pharmacokinetic; QD, once daily; QTcF, QT corrected for heart rate by Fridericia's cube root formula; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

In the phase 2 trial (Study 201), the Applicant selected brensocatib dosages of 10 mg and 25 mg once-daily (QD) for evaluation based on PD (plasma NE activity) and safety data from a phase 1 Study D6190C00001 conducted in healthy subjects. Following administration of brensocatib at 10 mg for 21 days, or at 25 mg or 40 mg for 28 days, the percent reduction in relative NE activity appeared to be dose-dependent, with an approximate plateau of effect reached at 25 mg (refer to Section 14.2.1). In Study 201, after 24 weeks of treatment, both brensocatib dosages of 10 mg and 25 mg QD demonstrated a prolongation in the time to first PEx, the primary endpoint, and reduction in the rate of PExs as compared to placebo, without a clear dose response relationship. Both brensocatib dose groups demonstrated an acceptable safety profile.

To further support dose selection for phase 3, the Applicant conducted simulations to relate brensocatib exposure to reductions in sputum NE and PEx. The Applicant's simulations suggested that doses below 10 mg were likely to be subtherapeutic while doses higher than 25 mg were unlikely to yield additional incremental efficacy. Therefore, both 10 mg and 25 mg QD dosages were selected for further evaluation in Study 301.

The Applicant performed exposure-response analysis using data from Studies 201 and 301 to support the proposed 25 mg QD dosage. However, as PK data are not available for approximately half of the subjects enrolled in Study 301, the interpretation of exposure-response efficacy analyses is limited. Refer to Sections 6.2 and 6.3 for detailed PK and efficacy assessments.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Results of Pooled Analyses, Studies 201 and 301

The evaluation of efficacy was based on the analyses of the individual trials. Pooled efficacy analyses are not presented.

6.2.2. Study 301

6.2.2.1. Design, Study 301

Study 301 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy, safety, and tolerability of oral brensocatib compared to placebo in adult and adolescent subjects aged 12 years and older with NCFB. Following screening, adult subjects were randomized 1:1:1 and adolescent subjects were randomized 2:2:1

to brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD, respectively, for a total 52 weeks. Randomization for adults was stratified based on:

- Geographic region, defined as North America, Europe, Japan, and the Rest of the World; enrollment targets were established with up to 13% of adults from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 25% each
- Sputum sample testing for the presence of *P. aeruginosa* at baseline
- Number of PEx, 2 or >3, in the previous 12 months.
- The trial protocol design, subject population, objectives, and endpoints are reviewed in Section 15.

The primary objective of Study 301 was to evaluate the efficacy of brensocatib 10 mg and 25 mg compared to placebo on the annualized rate of adjudicated PEx. Pulmonary exacerbations were defined by the Hill criteria (Hill et al. 2017) as having ≥3 of the following symptoms for at least 48 hours, resulting in a physician's decision to prescribe systemic antibiotics:

- Increased cough
- Increased sputum volume or change in sputum consistency
- Increased sputum purulence
- Increased breathlessness and/or decreased exercise tolerance
- Fatigue and/or malaise
- Hemoptysis

A minimum of 4 weeks must have occurred between the end date of one PEx and the start date of the next PEx. Any exacerbations that occurred less than 4 weeks from the PEx were not considered a new exacerbation. All PEx were adjudicated by a blinded independent adjudication committee composed of pulmonary physicians who reviewed all reported PEx to determine if they fulfilled the protocol definition.

The efficacy endpoints in the order of statistical hierarchy are listed below:

- Primary endpoint:
  - Annualized rate of PEx
- Key secondary endpoints:
  - Time to first PEx
  - Responder status for being exacerbation free
  - Change in postbronchodilator FEV1 at Week 52
  - Annualized rate of severe PEx
  - Change in QoL-B Respiratory Symptoms domain score at Week 52

Overall, the trial design and proposed endpoints are generally reasonable for the stated objectives.

6.2.2.2. Eligibility Criteria, Study 301

The eligibility criteria for Study 301 were reasonable to ensure inclusion of patients with symptomatic NCFB.

Key inclusion criteria included:

- Clinical history consistent with NCFB (cough, chronic sputum production and / or recurrent respiratory infections) that is confirmed by chest CT
- Adults only: Current sputum producer with a history of chronic expectoration of at least 3 months in the past 12 months.
- Mucopurulent or purulent sputum color
- Post-bronchodilator FEV1 of >30% predicted of normal value
- At least 2 PExs (adults) or 1 PEx (adolescents) in the past 12 months

Key exclusion criteria included:

- Primary diagnosis of chronic pulmonary obstructive disease (COPD) or asthma
- Bronchiectasis due to cystic fibrosis
- Supplemental oxygen requirement >12 hours per day
- Current treatment for a nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis
- Suffering an exacerbation 4 weeks before Screening
- Started oral or inhaled antibiotics as chronic treatment for NCFB <3 months prior to Screening
- Diagnosis of Papillon-Lefèvre syndrome or periodontal disease
- Current smoker

The overall eligibility criteria were reasonable for a phase 3 trial in NCFB. Study 301 included subjects with bronchiectasis etiologies of hypogammaglobulinemia, common variable immunodeficiency (CVID), and alpha-1 antitrypsin deficiency (AATD), thereby enrolling an NCFB population of greater diversity, compared to Study 201, which allows for broader generalizability of the results. Refer to Section 15.1.2 for a detailed review of the eligibility criteria.

6.2.2.3. Statistical Analysis Plan, Study 301

The statistical analysis plan for Study 301 is Version 1 dated April 19, 2024, and was submitted to the FDA on April 24, 2024. The primary efficacy endpoint was the annualized rate of pulmonary exacerbations through Week 52 for the intent-to-treat (ITT) analysis set, which was defined as all subjects who were randomized, excluding subjects from Ukraine because of war and subjects from site USA065 because of serious good clinical practice (GCP) noncompliance. The primary endpoint family included comparisons for both the brensocatib 25-mg group and brensocatib 10-mg group to the placebo group. Treatment policy strategy was used for the

intercurrent events of early treatment discontinuation and modification to standard of care. The primary analysis of all multiplicity-controlled endpoints used the treatment policy strategy and the ITT analysis set.

Primary Analysis

The primary analysis used negative binomial regression with a robust estimate for the covariance matrix. The model included treatment group, sputum sample being classified as positive or negative for *P. aeruginosa* at Screening Visit, the number of prior PEx (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as covariates and the logarithm of time at risk (time on study excluding the time during exacerbations) in years as an offset variable. The log link and an unstructured covariance matrix were used. In SAS PROC GENMOD, the OM option was used to adjust the coefficients for the least squares (LS) means to reflect the observed data.

From this model, the least squares mean rate, the standard error, and the corresponding 95% confidence intervals for each treatment group, as well as the model adjusted mean rate ratios of the brensocatib groups compared to the placebo group and the corresponding 95% confidence intervals were estimated.

Sensitivity and supplementary analyses were planned and conducted to evaluate the robustness of the primary analysis. For details, see Section 16.2.

Subgroup Analyses

Subgroup analyses were based on a similar negative binomial model as used for the primary analysis in the ITT analysis set. Section 15 includes a list of prespecified subgroups. The covariate of age group was not included in models for subgroup analyses. One model per subgroup parameter was fitted, omitting the fixed effect if identical to the subgroup or confounded with the subgroup. Similar post hoc analyses were conducted by the review team by etiology.

Secondary Endpoints

The first key secondary endpoint was the time to first pulmonary exacerbation and was analyzed using a Cox proportional hazards model. The model included the same covariates the analysis model for the primary endpoint (treatment group, sputum sample being classified as positive or negative for *P. aeruginosa* at Screening Visit, the number of prior PEx in the previous 12 months, stratification region, and age group) and a robust sandwich estimate for the covariance matrix. The hazard ratio, corresponding 95% confidence interval, and two-sided Wald p-value were estimated from this model.

The second key secondary endpoint was responder status for being exacerbation-free over the 52-week treatment period and was analyzed using a logistic regression model. The model included the same covariates as the analysis model for the primary endpoint. The odds ratio, corresponding 95% Wald confidence interval, and two-sided Wald chi-square test p-value were estimated from this model. For subjects who discontinued the study prior to Week 52 without experiencing a pulmonary exacerbation, multiple imputation was used to create 100 complete datasets, which were combined using Rubin's rules. Details of the multiple imputation procedure are included in Section 15.

Change from baseline post-BD FEV1 (L) at Week 52 was analyzed using a linear repeated measures mixed model with the same covariates as the analysis model for the primary endpoint, as well as baseline value, visit, and treatment by visit interaction. Repeated measures from Weeks 16, 28, 40, and 52 were included, and a compound symmetric covariance structure was used to produce a robust sandwich variance estimator. In SAS PROC MIXED, the OM option was used to adjust the coefficients for the least squares means to reflect the observed data. The least squares mean differences, corresponding 95% confidence intervals, and two-sided p-values were estimated from this model.

The annualized rate of severe pulmonary exacerbations was analyzed using the same method as for the primary endpoint.

Change from baseline in QoL-B RSS at Week 52 was analyzed using a linear repeated measures mixed model. The population for this endpoint was restricted to adults in the ITT analysis set. The model included the same covariates as the model for change from baseline in post-BD FEV1. Biweekly repeated measures were included, and a compound symmetric covariance structure was used to produce a robust sandwich variance estimator. In SAS PROC MIXED, the OM option was used to adjust the coefficients for the least squares means to reflect the observed data. The least squares mean differences, corresponding 95% confidence intervals, and two-sided p-values were estimated from this model.

Multiple Testing Procedure

The primary and key secondary endpoints were tested with an enhanced mixture-based gatekeeping procedure (Kordzakhia et al. 2018). There were six families constructed, one for each of the six efficacy endpoints. Each family had two null hypotheses, one for each of the brensocatib doses compared to placebo. Families 1-6 were in the order of endpoints described in Section 6.2.2.1. The gatekeeping procedure proceeded to the next family even if only one of the comparisons was significant in a particular family. A truncated version of the Hochberg test was used in Family 1. The Bonferroni test was used in Families 2 through 5. The Hochberg test was used in Family 6. The truncation parameters associated with this procedure were 0.9 for Family 1, 0 for Families 2-5, and 1 for Family 6. To ensure that the procedure was consistent with the logical restrictions among the null hypotheses, corresponding restrictions were imposed on the hypotheses within each intersection. Using this procedure, the adjusted p-value for a given null hypothesis was calculated based on unadjusted p-values from all 12 null hypotheses.

6.2.2.4. Results of Analyses, Study 301

Subject Enrollment and Disposition

Study 301 screened a total of 2296 subjects of which 1767 were randomized. Among the randomized, 44 Ukrainian subjects were discontinued because of the ongoing war in Ukraine and 2 subjects from Site USA065 were excluded from all analyses because of serious GCP noncompliance; therefore, a total of 1721 subjects were considered the ITT population. At the time of the primary database lock, 20 adolescent subjects were still in the treatment period, 122 subjects (99 adults, 23 adolescents) remained on study, though the majority were in the follow-up period, and 1381 subjects had completed both treatment and the trial. The safety population included 1719 subjects who had received at least one dose of trial drug. The subject enrollment and disposition for Study 301 are reviewed in Table 8.

Table 8. Subject Disposition, Study 301[1]

Disposition	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563	Total N=1721
Screened				2296
Screen failure				529
Screen failure reason				
Did not meet inclusion/exclusion criteria				474
Withdrawal of consent				49
Other				6
Randomized	595	593	579	1767
Discontinued due to war in Ukraine	12	17	15	44
Excluded due to serious GCP noncompliance	0	1	1	2
Analysis set				
Intent-to-treat (ITT)	583 (100)	575 (100)	563 (100)	1721 (100)
Safety	582 (99.8)	574 (99.8)	563 (100)	1719 (99.9)
Study completion status				
No	78 (13.4)	65 (11.3)	75 (13.3)	218 (12.7)
Ongoing	47 (8.1)	44 (7.7)	31 (5.5)	122 (7.1)
Yes	458 (78.6)	466 (81.0)	457 (81.2)	1381 (80.2)
Study discontinuation reason				
Adverse event	10 (1.7)	10 (1.7)	9 (1.6)	29 (1.7)
Death	2 (<1)	4 (<1)	8 (1.4)	14 (<1)
Lost to follow-up	10 (1.7)	2 (<1)	4 (<1)	16 (<1)
Physician decision	2 (<1)	2 (<1)	3 (<1)	7 (<1)
Protocol deviation	1 (<1)	3 (<1)	2 (<1)	6 (<1)
Withdrawal by subject	40 (6.9)	32 (5.6)	37 (6.6)	109 (6.3)
Other	13 (2.2)	12 (2.1)	12 (2.1)	37 (2.1)
Treatment completion status				
No	72 (12.3)	62 (10.8)	73 (13.0)	207 (12.0)
Ongoing	9 (1.5)	7 (1.2)	4 (<1)	20 (1.2)
Yes	501 (85.9)	505 (87.8)	486 (86.3)	1492 (86.7)
Treatment discontinuation reason				
Adverse event	25 (4.3)	22 (3.8)	23 (4.1)	70 (4.1)
Death	1 (<1)	3 (<1)	3 (<1)	7 (<1)
Lack of efficacy	1 (<1)	3 (<1)	5 (<1)	9 (<1)
Lost to follow-up	8 (1.4)	0	4 (<1)	12 (<1)
Non-compliance with study drug	0	1 (<1)	2 (<1)	3 (<1)
Physician decision	4 (<1)	3 (<1)	3 (<1)	10 (<1)
Protocol deviation	0	2 (<1)	1 (<1)	3 (<1)
Withdrawal by subject	32 (5.5)	27 (4.7)	31 (5.5)	90 (5.2)
Other	1 (<1)	1 (<1)	1 (<1)	3 (<1)

Source: Clinical Study Report Table 5 and Table 8 (Pages 30-31, 33); findings reproduced by statistical reviewer using adsl.xpt
[1] All values expressed as n(%) unless stated otherwise. Percentages out of N.
Abbreviations: GCP, good clinical practice, ITT, intent-to-treat, N, number of subjects in the ITT analysis set, QD, once daily

There were no significant differences observed between treatment groups in the number of subjects who discontinued treatment or discontinued the trial. Similarly, there were no differences between groups in the reasons for treatment or study discontinuation with the most common reason for either being "withdrawal by subject" (Table 8). The small differences in treatment discontinuation and study withdrawal are unlikely to substantially affect the interpretation of the safety or efficacy results.

Subject Demographics

The baseline demographics for Study 301 are summarized in Table 9. Overall, the population had a mean age of 60.2 years (range 12 to 85 years), and the majority were female (64.3%), white (73.6%), never smokers (70.4%). There were no significant imbalances between treatment groups in baseline demographics. The enrolled population was generally representative of the disease population.

Table 9. Baseline Demographics and Clinical Characteristics, ITT Population, Study 301

Demographic/ Characteristic	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563	Total N=1721
Age				
Mean (SD)	59.8 (15.9)	60.6 (15.8)	60.0 (15.4)	60.2 (15.7)
Median	63.0	65.0	63.0	64.0
IQR	52.0, 72.0	52.0, 72.0	51.0, 71.0	52.0, 72.0
Min, max	12.0, 85.0	12.0, 85.0	12.0, 85.0	12.0, 85.0
Age group, n(%)				
Adolescent	17 (2.9)	16 (2.8)	8 (1.4)	41 (2.4)
Adult	566 (97.1)	559 (97.2)	555 (98.6)	1680 (97.6)
Sex, n(%)				
Female	385 (66.0)	360 (62.6)	362 (64.3)	1107 (64.3)
Male	198 (34.0)	215 (37.4)	201 (35.7)	614 (35.7)
Race, n(%)				
American Indian or Alaska Native	8 (1.4)	6 (1.0)	9 (1.6)	23 (1.3)
Asian	63 (10.8)	64 (11.1)	64 (11.4)	191 (11.1)
Black or African American	2 (<1)	5 (<1)	3 (<1)	10 (<1)
Multiple	15 (2.6)	11 (1.9)	11 (2.0)	37 (2.1)
Native Hawaiian or other Pacific Islander	1 (<1)	0	1 (<1)	2 (<1)
Not reported/unknown	48 (8.2)	46 (8.0)	59 (10.5)	153 (8.9)
White	431 (73.9)	430 (74.8)	405 (71.9)	1266 (73.6)
Other	15 (2.6)	13 (2.3)	11 (2.0)	39 (2.3)
Ethnicity, n(%)				
Hispanic or Latino	177 (30.4)	164 (28.5)	170 (30.2)	511 (29.7)
Not Hispanic or Latino	391 (67.1)	397 (69.0)	373 (66.3)	1161 (67.5)
Geographical Region, n(%)				
Europe	231 (39.6)	221 (38.4)	221 (39.3)	673 (39.1)
Japan	30 (5.1)	28 (4.9)	29 (5.2)	87 (5.1)
North America	84 (14.4)	83 (14.4)	81 (14.4)	248 (14.4)
Rest of world	238 (40.8)	243 (42.3)	232 (41.2)	713 (41.4)
BSI score, n(%)				
≤4	136 (23.3)	150 (26.1)	148 (26.3)	434 (25.2)
5-8	275 (47.2)	239 (41.6)	220 (39.1)	734 (42.6)
≥9	168 (28.8)	182 (31.7)	195 (34.6)	545 (31.7)
Number of PEx in previous 12 months, n(%)				
<3	411 (70.5)	412 (71.7)	396 (70.3)	1219 (70.8)
≥3	172 (29.5)	163 (28.3)	167 (29.7)	502 (29.2)
Antibiotic use at baseline, n(%)	146 (25.0)	154 (26.8)	133 (23.6)	433 (25.2)
Macrolide use at baseline, n(%)	110 (18.9)	114 (19.8)	105 (18.7)	329 (19.1)
Pa colonization at baseline, n(%)				
Negative	380 (65.2)	370 (64.3)	364 (64.7)	1114 (64.7)
Positive	203 (34.8)	205 (35.7)	199 (35.3)	607 (35.3)

Demographic/ Characteristic	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563	Total N=1721
Baseline FEV1% predicted post-bronchodilator, n(%)				
<50%	101 (17.3)	102 (17.7)	98 (17.4)	301 (17.5)
≥50%	478 (82.0)	469 (81.6)	465 (82.6)	1412 (82.0)
Baseline eosinophil count, n(%)				
<300/mm^3	465 (79.8)	461 (80.2)	452 (80.3)	1378 (80.1)
≥300/mm^3	115 (19.7)	111 (19.3)	106 (18.8)	332 (19.3)
History of asthma, n(%)	101 (17.3)	109 (19.0)	111 (19.7)	321 (18.7)
History of COPD, n(%)	77 (13.2)	83 (14.4)	102 (18.1)	262 (15.2)
Use of inhaled steroids, n(%)	324 (55.6)	324 (56.3)	352 (62.5)	1000 (58.1)
Hospitalized in prior 24 months for PEx, n(%)	146 (25.0)	133 (23.1)	142 (25.2)	421 (24.5)

Source: Clinical Study Report Table 9 and Table 10 (Pages 34-35, 36-38); findings reproduced by statistical reviewer using adsl.xpt
Abbreviations: BSI, bronchiectasis severity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; IQR, interquartile range, ITT, intent-to-treat, max, maximum; min, minimum; N, number of subjects; n, number of subjects within specific demographic or with specific characteristic; Pa, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation; QD, once daily, SD, standard deviation

The overall baseline NCFB characteristics (Table 9) were balanced between the treatment groups and generally represented the heterogeneity of disease features and severity that is characteristic of NCFB. The overall population had a mean post-BD FEV1 of 73.5% predicted, consistent with mild obstruction. The majority of the population had a post-BD FEV1≥50% (82.0%), ≤2 pulmonary exacerbations in the preceding 12 months prior to enrollment (70.8%), and they were negative for *P. aeruginosa* (64.7%). Half the population was using inhaled steroids (58.1%), while chronic macrolide use was uncommon (19.1%). The BSI score was calculated at baseline and used as a metric to assess NCFB severity, where a score of ≤4 is mild disease, 5 to 8 is moderate disease and ≥9 is severe disease. The mean BSI was 7.1 (range 1 to 20) with most patients having moderate (42.6%) to severe (31.7%) disease at baseline. For details on the BSI scoring system, refer to Section 15.1.2.

COPD and asthma history, documented for the assessment of the exclusion criteria (refer to Section 6.2.2.2), were secondary diagnoses in 15.2% and 18.7% of subjects, respectively. Review of underlying bronchiectasis etiologies found more than half the subjects (n=1006; 58.5%) classified as "Other" with free-text entry for either the known or presumed etiology. After "Other," the next most common etiologic categories were pneumonia/childhood infections (29.3%) and primary ciliary dyskinesia (6.9%). Among the 1,006 subjects classified as "Other", review of the free-text responses found the majority were defined as idiopathic or unknown (62.7%) or secondary to a history of infection(s) (28.5%). Most of the infections were not known (29.6%) or were documented as secondary to mycobacterial (17.8%) or viral (4.9%) pathogens.

Overall, the enrolled population was sufficiently representative of the NCFB population to support the generalizability of trial results.

Analysis of Efficacy-Primary Endpoint

Table 10 summarizes the efficacy results for the annualized rate of pulmonary exacerbations through Week 52 for the primary endpoint comparison between both brensocatib treatment groups and the placebo group. After adjusting for sputum sample classification as positive or

negative for *P. aeruginosa* at screening, the number of prior PEx (<3 or ≥3) in the previous 12 months, stratification region, and age group, the estimated least squares mean annualized rate of pulmonary exacerbations was lower in both the brensocatib 10 mg (LS mean = 1.02, 95% CI = 0.91,1.12) and brensocatib 25 mg (LS mean = 1.04, 95% CI = 0.93, 1.16) groups compared to placebo (LS mean = 1.29, 95% CI = 1.16, 1.43). The rate ratio compared to placebo was 0.79 (95% CI = 0.68, 0.92) for the brensocatib 10-mg group and 0.81 (95% CI = 0.69, 0.94) for the brensocatib 25-mg group, both statistically significant. Figure 1 displays the cumulative mean number of pulmonary exacerbations through Week 52 by treatment group and is supportive of the primary analysis.

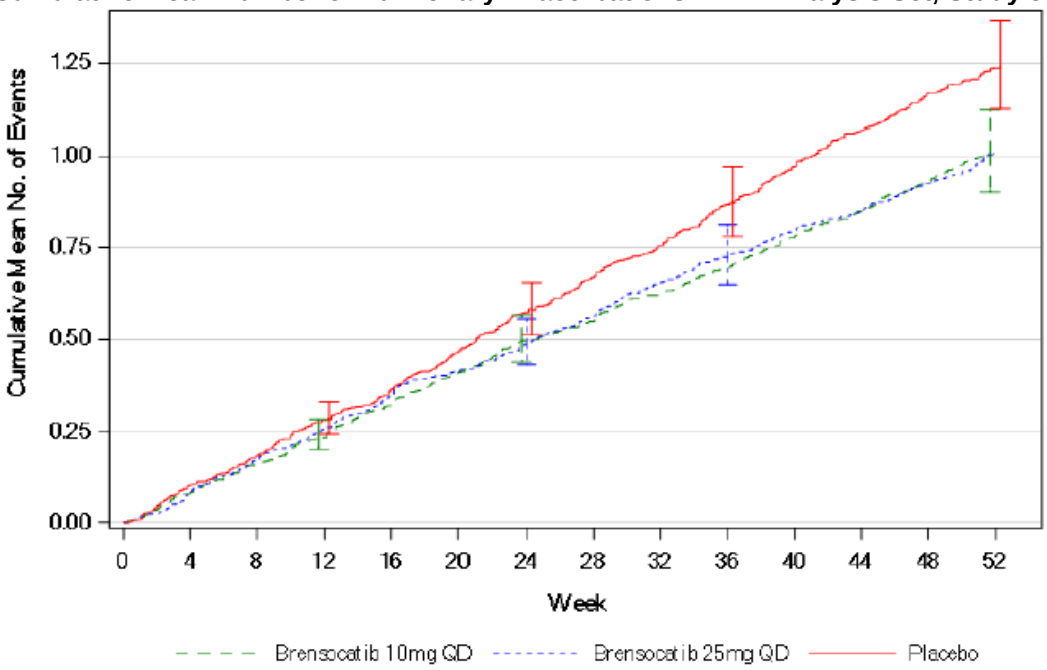
Table 10. Primary Analysis: Annualized Rate of Pulmonary Exacerbations Through Week 52 in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Number of subjects with exacerbation events, n(%)			
0	291 (49.9)	287 (49.9)	239 (42.5)
1	153 (26.2)	146 (25.4)	145 (25.8)
2	63 (10.8)	67 (11.7)	88 (15.6)
≥3	76 (13.0)	75 (13.0)	91 (16.2)
Annualized rate of PEx[1] (95% CI)	1.02 (0.91, 1.13)	1.04 (0.93, 1.16)	1.29 (1.16, 1.43)
Rate ratio compared to placebo[1] (95% CI)	0.79 (0.68, 0.92)	0.81 (0.69, 0.94)	-
Unadjusted p-value[1]	0.002	0.005	-
Adjusted p-value[2]	0.004	0.005	-

Source: Clinical Study Report Table 15 and Table 16 (Pages 45, 46); findings reproduced by the statistical reviewer using adces.xpt
[1] The negative binomial regression model included treatment group, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as covariates and the logarithm of time at risk in years as an offset variable.
[2] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, ITT, intent-to-Treat, N, number of subjects; n, number of subjects within specific parameter; PEx, pulmonary exacerbation, QD, once daily

The review team was able to replicate the Applicant's analyses of the primary endpoint, and the results demonstrate superiority of both doses compared with placebo in Study 301.

Figure 1. Cumulative Mean Number of Pulmonary Exacerbations in ITT Analysis Set, Study 301



Number of Participants														
Brensocatib 10mg QD	583	582	582	576	570	565	564	555	546	540	533	529	522	516
Brensocatib 25mg QD	575	572	568	566	563	552	550	543	540	537	528	523	520	515
Placebo	563	562	556	551	547	544	539	534	529	522	519	509	507	499

Source: Clinical Study Report Figure 2 (Page 47)
Abbreviations: ITT, intent-to-treat, No., number; QD, once daily

Sensitivity and supplementary analyses had similar results to the primary analysis and support the robustness of the primary analysis. Further discussion of these analyses is found in Section 16.2.

Analysis of Efficacy-Secondary Endpoints

Table 11 presents the results for the time to first pulmonary exacerbation through Week 52 in Study 301. After adjusting for sputum sample classification as positive or negative for *P. aeruginosa* at screening, the number of prior PEx in the previous 12 months, stratification region, and age group, the median time in weeks to first PEx was smaller in the placebo group (36.7, 95% CI = 31.1, 41.4) than in the brensocatib 10 mg (49.0, 95% CI = 40.0, Not Estimable) and brensocatib 25 mg (50.7, 95% CI = 37.6, Not Estimable) groups. The hazard ratio compared to placebo was 0.81 (95% CI = 0.70, 0.95) for the brensocatib 10-mg group and 0.83 (95% CI = 0.70, 0.97) for the brensocatib 25-mg group, both statistically significant.

Table 11. Secondary Analysis: Time to First Pulmonary Exacerbation Through Week 52 in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Subjects with PExs, n(%)	292 (50.1)	288 (50.1)	324 (57.5)
Median time to first PEx in weeks[1] (95% CI)	49.0 (40.0, NE)	50.7 (37.6, NE)	36.7 (31.1, 41.4)
Hazard ratio compared to placebo[2] (95% CI)	0.81 (0.70, 0.95)	0.83 (0.70, 0.97)	-
Unadjusted p-value[2]	0.01	0.02	-
Adjusted p-value[3]	0.02	0.04	-

Source: Clinical Study Report Table 15 and Table 18 (Pages 45, 58-59); findings reproduced by the statistical reviewer using adtte.xpt
[1] Kaplan Meier estimates were used for the median time to first PEx.
[2] The Cox proportional hazards model included treatment group, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as covariates and a robust sandwich estimate for the covariance matrix.
[3] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, ITT, intent-to-treat, N, number of subjects; n, number of subjects within specific parameter; NE, not estimable, PEx, pulmonary exacerbation, QD, once daily

Table 12 summarizes the subjects who were responders, defined as being exacerbation-free over the 52-week treatment period in Study 301. The number of subjects with an observed PEx was higher in the placebo group (324, 57.7%) than in the brensocatib 10-mg group (292, 50.1%) and brensocatib 25-mg group (288, 50.1%). Subjects who were censored prior to Week 52 required imputation to determine responder status. The average number of responders over 100 imputed datasets was lower in the placebo group (227, 40.3%) compared to the brensocatib 10-mg group (283, 48.5%) and brensocatib 25-mg group (279, 48.5%). The odds ratio of responders versus non-responders compared to placebo was 1.41 (95% CI = 1.11, 1.81) for the brensocatib 10-mg group and 1.40 (95% CI = 1.10, 1.79) for the brensocatib 25-mg group, both statistically significant.

Table 12. Secondary Analysis: Responder Status For Exacerbation-Free Over 52-Week Treatment Period in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Responders, average of 100 imputed datasets, n(%)	283 (48.5)	279 (48.5)	227 (40.3)
Non-responders, average of 100 imputed datasets, n(%)	300 (51.5)	296 (51.5)	336 (59.7)
Number of subjects with PEx, pre-imputation, n(%)	292 (50.1)	288 (50.1)	324 (57.5)
Odds ratio compared to placebo[1] (95% CI)	1.41 (1.11, 1.81)	1.40 (1.10, 1.79)	-
Unadjusted p-value[1]	0.006	0.007	-
Adjusted p-value[2]	0.02	0.04	-

Source: Clinical Study Report Table 15 and Table 19 (Pages 45, 60-61); findings reproduced by the statistical reviewer using adtte.xpt
[1] Primary analysis based on 100 logistic regression models which included treatment group, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as covariates. Rubin's rules were used to combine parameter estimates and exponentiated to estimate the odds ratio.
[2] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, ITT, intent-to-treat, N, number of subjects; n, number of subjects within specific parameter; PEx, pulmonary exacerbation; QD, once daily

Table 13 summarizes the change from baseline in post-BD FEV1 in liters at Week 52. After adjusting for sputum sample classification as positive or negative for *P. aeruginosa* at screening,

the number of prior PEx (<3 or ≥3) in the previous 12 months, stratification region, age group, visit, visit by treatment group, and baseline value, the estimated least squares mean change from baseline in post-bronchodilator FEV1 in liters at Week 52 was less negative in both the brensocatib 10 mg (−0.050, SE =0.009) and brensocatib 25 mg (−0.024, SE =0.010) groups compared to placebo (−0.062, SE =0.009). The difference in least squares means compared to placebo was 0.011 L (95% CI = -0.014, 0.037) for the brensocatib 10-mg group and 0.038 L (95% CI = 0.011, 0.065) for the brensocatib 25-mg group, only the latter of which was statistically significant.

Table 13. Secondary Analysis: Change From Baseline in Post-Bronchodilator FEV1 (L) at Week 52 in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
LS mean[1] (SE)	-0.050 (0.009)	-0.024 (0.010)	-0.062 (0.009)
LS mean difference compared to placebo[1] (95% CI)	0.011 (−0.014, 0.037)	0.038 (0.011, 0.065)	-
Unadjusted p-value[1]	0.38	0.005	-
Adjusted p-value[2]	0.38	0.04	-

Source: Clinical Study Report Table 15 and Table 20 (Pages 45, 62); findings reproduced by the statistical reviewer using adre.xpt
[1] The linear repeated measures model included treatment group, visit, treatment group by visit interaction, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), age group (adult, adolescent), and baseline value as covariates and a compound symmetric robust sandwich variance estimator. Repeated measures from Weeks 16, 28, 40, and 52 were included in the model. Baseline was the most recent non-missing assessment determined as best effort prior to the first dose of the investigational product. Only best efforts were analyzed.
[2] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, FEV1, forced expiratory volume in 1 second, ITT, intent-to-treat, L, liters, LS, least squares, N, number of subjects; QD, once daily, SE, standard error

Although the difference in least squares mean between placebo and the brensocatib 25-mg groups is statistically significant, the numeric differences are quite small. The least squares mean for the brensocatib 25-mg group was minimal at 0.038 L or 38 mL. Additionally, the difference in least squares mean changes between brensocatib 10-mg and brensocatib 25-mg groups, demonstrates a similarly small difference of 0.026 L (26 mL). Refer to Section 6.3.1 for additional discussion.

Table 14 summarizes the annualized rate of severe PEx through Week 52. After adjusting for sputum sample being classified as positive or negative for *P. aeruginosa* at screening, the number of prior PEx (<3 or ≥3) in the previous 12 months, stratification region, and age group, the estimated LS mean annualized rate of PExs was lower in both the brensocatib 10 mg (LS mean = 0.14, 95% CI = 0.10, 0.18) and brensocatib 25 mg (LS mean = 0.14, 95% CI = 0.11, 0.18) groups compared to placebo (LS mean = 0.19, 95% CI = 0.14, 0.24). The rate ratio compared to placebo was 0.74 (95% CI = 0.51, 1.09) for the brensocatib 10-mg group and 0.74 (95% CI = 0.52, 1.06) for the brensocatib 25-mg group, neither of which were statistically significant.

Table 14. Secondary Analysis: Annualized Rate of Severe Pulmonary Exacerbations Through Week 52 in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=583	Brensocatib 25 mg N=575	Placebo N=563
Number of subjects with exacerbation events, n(%)			
0	522 (89.5)	512 (89.0)	487 (86.5)
1	48 (8.2)	49 (8.5)	53 (9.4)
2	7 (1.2)	12 (2.1)	16 (2.8)
≥3	6 (1.0)	2 (0.3)	7 (1.2)
Annualized rate of PEx[1] (95% CI)	0.14 (0.10, 0.18)	0.14 (0.11, 0.18)	0.19 (0.14, 0.24)
Rate ratio compared to placebo[1] (95% CI)	0.74 (0.51, 1.09)	0.74 (0.52, 1.06)	-
Unadjusted p-value[1]	0.13	0.11	-
Adjusted p-value[2]	0.38	0.21	-

Source: Clinical Study Report Table 15 and Table 21 (Pages 45, 63-64); findings reproduced by the statistical reviewer using adces.xpt
[1] The negative binomial regression model included treatment group, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as covariates and the logarithm of time at risk in years as an offset variable.
[2] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, ITT, intent-to-treat, N, number of subjects; n, number of subjects with specific parameter; PEx, pulmonary exacerbation, QD, once daily

Table 15 summarizes the change from baseline in QoL-B RSS at Week 52. After adjusting for sputum sample classification as positive or negative for *P. aeruginosa* at screening, the number of prior PEx (<3 or ≥3) in the previous 12 months, stratification region, age group, visit, visit by treatment group, and baseline value, the estimated least squares mean change from baseline in QoL-B RSS at Week 52 was higher in both the brensocatib 10-mg and brensocatib 25-mg groups compared to placebo. The difference in least squares means compared to placebo was 2.03 (95% CI = -0.08, 4.14) for the brensocatib 10-mg group and 3.77 (95% CI = 1.68, 5.85) for the brensocatib 25-mg group, neither of which was statistically significant. Refer to Section 6.3.3 and Section 16.1.4 for additional discussion of the treatment effects observed for this instrument.

Table 15. Secondary Analysis: Change From Baseline in QoL-B Respiratory Symptoms Domain Score at Week 52 in Adult Subjects in ITT Analysis Set, Study 301

Parameter	Brensocatib 10 mg N=566	Brensocatib 25 mg N=559	Placebo N=555
LS mean[1] (SE)	6.84 (0.77)	8.58 (0.76)	4.81 (0.75)
LS mean difference compared to placebo[1] (95% CI)	2.03 (−0.08, 4.14)	3.77 (1.68, 5.85)	-
Unadjusted p-value[1]	0.06	0.0004	-
Adjusted p-value[2]	0.38	0.21	-

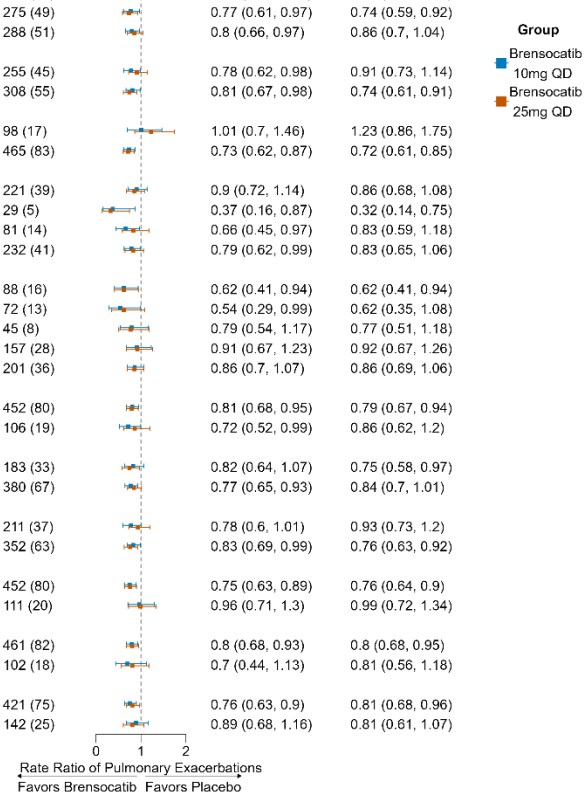
Source: Clinical Study Report Table 15 and Table 22 (Pages 45, 65); findings reproduced by the statistical reviewer using adqs.xpt
[1] The linear repeated measures model included treatment group, visit, treatment group by visit interaction, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, stratification region (North America, Europe, Japan, and the Rest of the World), age group (adult, adolescent), and baseline value as covariates and a compound symmetric robust sandwich variance estimator. Biweekly repeated measures were included in the model. Baseline was defined as the most recent assessment on or before study Day 1.
[2] Adjusted p-value using enhanced mixture-based gatekeeping procedure.
Abbreviations: CI, confidence interval, ITT, intent-to-treat, LS, least squares, N, number of subjects; QD, once daily, QoL-B, Quality of Life Questionnaire - Bronchiectasis, SE, standard error

Analysis of Efficacy-Subgroup Analyses

The prespecified subgroup analyses of the annualized rate of PEx are presented in Table 16. The rate ratios of the annualized rate of PEx through Week 52 comparing both brensocatib arms to pooled placebo were generally consistent across the prespecified subgroups. Point estimates favored brensocatib for most subgroups, although confidence intervals included the null value of 1 for many subgroups. The exception is the subgroup with baseline post-bronchodilator percent predicted FEV1 of less than 50%, which slightly favored placebo and had wide confidence intervals which crossed the null value. Clinical interpretation of this subgroup is limited by the wide confidence intervals, likely a function of small sample size.

Table 16. Subgroup Analysis: Forest Plot of Rate Ratio of Pulmonary Exacerbations Through Week 52 Between Brensocatib and Placebo in ITT Analysis Set, Study 301

Variable	Brensocatib 10mg QD, n (%)	Brensocatib 25mg QD, n (%)	Placebo, n (%)	Rate Ratio (95% CI) for 10mg arm	Rate Ratio (95% CI) for 25mg arm
Overall	583 (100)	575 (100)	563 (100)	0.79 (0.68, 0.92)	0.81 (0.69, 0.94)
Age Group					
12 To <18 Years	17 (3)	16 (3)	8 (1)	0.41 (0.11, 1.58)	0.73 (0.2, 2.68)
18 To <65 Years	289 (50)	257 (45)	295 (52)	0.81 (0.66, 0.99)	0.7 (0.57, 0.86)
>=65 Years	277 (48)	302 (53)	260 (46)	0.79 (0.63, 0.99)	0.93 (0.74, 1.15)
<75 Years	500 (86)	491 (85)	470 (83)	0.81 (0.69, 0.95)	0.79 (0.68, 0.93)
>=75 Years	83 (14)	84 (15)	93 (17)	0.61 (0.4, 0.94)	0.89 (0.59, 1.34)
Adult	566 (97)	559 (97)	555 (99)	0.8 (0.69, 0.93)	0.8 (0.69, 0.93)
Sex					
Female	385 (66)	360 (63)	362 (64)	0.81 (0.68, 0.96)	0.83 (0.7, 1)
Male	198 (34)	215 (37)	201 (36)	0.75 (0.57, 1)	0.75 (0.57, 0.98)
Race					
Asian	63 (11)	64 (11)	64 (11)	0.4 (0.23, 0.67)	0.41 (0.24, 0.7)
White	431 (74)	430 (75)	405 (72)	0.79 (0.67, 0.94)	0.79 (0.67, 0.93)
Ethnicity					
Hispanic Or Latino	177 (30)	164 (29)	170 (30)	0.94 (0.7, 1.26)	0.92 (0.69, 1.24)
Not Hispanic Or Latino	391 (67)	397 (69)	373 (66)	0.73 (0.61, 0.87)	0.77 (0.64, 0.91)
Number Of Pulmonary Exacerbations In Prior 12 Months					
<3	411 (70)	412 (72)	396 (70)	0.73 (0.6, 0.89)	0.78 (0.64, 0.95)
>=3	172 (30)	163 (28)	167 (30)	0.89 (0.72, 1.11)	0.85 (0.67, 1.07)
Chronic Use Of Antiobiotics At Baseline					
No	437 (75)	421 (73)	430 (76)	0.8 (0.66, 0.96)	0.82 (0.68, 0.98)
Yes	146 (25)	154 (27)	133 (24)	0.76 (0.59, 0.97)	0.74 (0.57, 0.96)
Maintenance Use Of Macrolides At Baseline					
No	473 (81)	461 (80)	458 (81)	0.78 (0.66, 0.93)	0.8 (0.67, 0.94)
Yes	110 (19)	114 (20)	105 (19)	0.79 (0.58, 1.06)	0.79 (0.58, 1.08)
Pa Colonization At Baseline					
Negative	380 (65)	370 (64)	364 (65)	0.81 (0.67, 0.98)	0.77 (0.63, 0.94)
Positive	203 (35)	205 (36)	199 (35)	0.75 (0.59, 0.95)	0.88 (0.7, 1.1)
Pooled BSI Group					
4 Or Less	136 (23)	150 (26)	148 (26)	0.77 (0.55, 1.07)	0.69 (0.5, 0.95)
5-8	275 (47)	239 (42)	220 (39)	0.71 (0.56, 0.89)	0.77 (0.6, 0.97)
9 Or More	168 (29)	182 (32)	195 (35)	0.92 (0.72, 1.17)	0.92 (0.73, 1.17)
<Median	286 (49)	278 (48)	275 (49)	0.77 (0.61, 0.97)	0.74 (0.59, 0.92)
>=Median	293 (50)	293 (51)	288 (51)	0.8 (0.66, 0.97)	0.86 (0.7, 1.04)
BE-CT score					
<Median	274 (47)	273 (47)	255 (45)	0.78 (0.62, 0.98)	0.91 (0.73, 1.14)
>=Median	309 (53)	302 (53)	308 (55)	0.81 (0.67, 0.98)	0.74 (0.61, 0.91)
Baseline FEV1 % predicted post-bronchodilator					
<50%	101 (17)	102 (18)	98 (17)	1.01 (0.7, 1.46)	1.23 (0.86, 1.75)
>=50%	478 (82)	469 (82)	465 (83)	0.73 (0.62, 0.87)	0.72 (0.61, 0.85)
Stratification Region					
Europe	231 (40)	221 (38)	221 (39)	0.9 (0.72, 1.14)	0.86 (0.68, 1.08)
Japan	30 (5)	28 (5)	29 (5)	0.37 (0.16, 0.87)	0.32 (0.14, 0.75)
North America	84 (14)	83 (14)	81 (14)	0.66 (0.45, 0.97)	0.83 (0.59, 1.18)
Rest Of World	238 (41)	243 (42)	232 (41)	0.79 (0.62, 0.99)	0.83 (0.65, 1.06)
Geographic Region					
Asian Countries	81 (14)	91 (16)	88 (16)	0.62 (0.41, 0.94)	0.62 (0.41, 0.94)
Eastern Europe	75 (13)	68 (12)	72 (13)	0.54 (0.29, 0.99)	0.62 (0.35, 1.08)
Oceania	37 (6)	54 (9)	45 (8)	0.79 (0.54, 1.17)	0.77 (0.51, 1.18)
South America	174 (30)	157 (27)	157 (28)	0.91 (0.67, 1.23)	0.92 (0.67, 1.26)
Western Countri	216 (37)	205 (36)	201 (36)	0.86 (0.7, 1.07)	0.86 (0.69, 1.06)
Baseline Eosinophil Count					
<300/Mm3	465 (80)	461 (80)	452 (80)	0.81 (0.68, 0.95)	0.79 (0.67, 0.94)
>=300/Mm3	115 (20)	111 (19)	106 (19)	0.72 (0.52, 0.99)	0.86 (0.62, 1.2)
Smoking Status					
Former Smoker	164 (28)	163 (28)	183 (33)	0.82 (0.64, 1.07)	0.75 (0.58, 0.97)
Never Smoked	419 (72)	412 (72)	380 (67)	0.77 (0.65, 0.93)	0.84 (0.7, 1.01)
Use Of Inhaled Steroids					
No	259 (44)	251 (44)	211 (37)	0.78 (0.6, 1.01)	0.93 (0.73, 1.2)
Yes	324 (56)	324 (56)	352 (63)	0.83 (0.69, 0.99)	0.76 (0.63, 0.92)
History Of Asthma					
No	482 (83)	466 (81)	452 (80)	0.75 (0.63, 0.89)	0.76 (0.64, 0.9)
Yes	101 (17)	109 (19)	111 (20)	0.96 (0.71, 1.3)	0.99 (0.72, 1.34)
History of COPD					
No	506 (87)	492 (86)	461 (82)	0.8 (0.68, 0.93)	0.8 (0.68, 0.95)
Yes	77 (13)	83 (14)	102 (18)	0.7 (0.44, 1.13)	0.81 (0.56, 1.18)
Hospitalized In Prior 24 Months					
No	437 (75)	442 (77)	421 (75)	0.76 (0.63, 0.9)	0.81 (0.68, 0.96)
Yes	146 (25)	133 (23)	142 (25)	0.89 (0.68, 1.16)	0.81 (0.61, 1.07)



Source: Clinical Study Report Figures 4 and 5 (Pages 52-57); findings reproduced by the statistical reviewer using adces.xpt
Abbreviations: BE-CT, bronchiectasis computed tomography; BSI, bronchiectasis severity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; ITT, intent-to-treat; Pa, *Pseudomonas aeruginosa*; QD, once daily

6.2.3. Study 201

6.2.3.1. Design, Study 201

Study 201 was a phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of oral brensocatib 10 mg and 25 mg QD compared to placebo in subjects aged 18 years and older with NCFB. Following screening, subjects were randomized 1:1:1 to one of the three treatment arms to receive assigned treatment for 24 weeks followed by a 4-week follow-up period. Randomization was stratified based on whether the sputum culture at screening was positive for *P. aeruginosa* and whether the subject was on maintenance use of macrolides. The review of the trial protocol design, subject population, objectives, and endpoints are reviewed in Section 15.

The primary objective of Study 201 was to evaluate the efficacy of brensocatib on time to first pulmonary exacerbation compared to placebo over the 24-week treatment period. The efficacy endpoints are listed below:

- Primary endpoint:
  - Time to first pulmonary exacerbation
- Secondary endpoints:
  - Change from baseline in QOL-B RSS at 24-weeks
  - Change from Screening in post-bronchodilator FEV1 at 24-weeks
  - Rate of pulmonary exacerbations (number of events over person-time) at 24-weeks

Change in concentration of active NE in sputum from pre-treatment to on-treatment was listed as a secondary endpoint; however, this endpoint is considered an exploratory pharmacodynamic endpoint. The primary endpoint is the focus of the review of Study 201 for substantial evidence of effectiveness. The secondary endpoints are viewed as supportive and so the presented analyses will be descriptive. Overall, the trial design and proposed endpoints are generally reasonable for the stated objectives.

6.2.3.2. Eligibility Criteria, Study 201

The eligibility criteria for Study 201 were reasonable to ensure inclusion of patients with symptomatic NCFB.

Key inclusion criteria included:

- Diagnosed with NCFB confirmed by chest CT
- Current sputum producer with history of chronic expectoration and able to provide a sample
- Documentation of at least 2 pulmonary exacerbations, defined as the need for antibiotic prescription by a physician for signs and symptoms of respiratory infections, in the last 12 months

Key exclusion criteria included:

- Primary diagnosis of COPD or asthma
- Bronchiectasis due to cystic fibrosis, hypogammaglobulinemia, CVID, or AATD
- Current treatment for a nontuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis
- Acute infection requiring treatment within 4 weeks of Screening (or 12 weeks if prescribed a macrolide)
- Taking cyclic doses of antibiotics as chronic treatment for NCFB or chronic oral or inhaled antibiotics <6 months prior to Baseline
- Concomitant medications with the potential to cause hyperkeratosis
- Any conditions associated with the onset of non-hereditary palmoplantar hyperkeratosis
- Periodontal disease diagnosed by a periodontist or dentist
- Current smoker

The overall eligibility criteria were reasonable for a phase 2 trial in NCFB. However, unlike Study 301, patients with bronchiectasis etiologies such as hypogammaglobulinemia, CVID, and AATD were excluded, which may limit the generalizability of the results. Refer to Section 15.2.2 for review of full eligibility criteria.

6.2.3.3. Statistical Analysis Plan, Study 201

The statistical analysis plan for Study 201 was Version 1 dated January 9, 2020, and was submitted to the FDA on August 7, 2020. The primary efficacy endpoint was the time to first pulmonary exacerbation over the 24-week treatment period for the ITT analysis set, which included all subjects who were randomized. The ITT analysis set was used for analyses unless otherwise specified. Secondary endpoint analyses are discussed in Section 15, with results in Section 16.

Primary Analysis

The time to first PEx was calculated as the number of days from the date of randomization to the date of first documentation of a PEx. The primary analysis used the stratified log rank test, stratified by *P. aeruginosa* colonization status and maintenance antibiotic use at baseline. Median survival time was estimated with Kaplan Meier product limit estimators. Subjects who did not have a pulmonary exacerbation during the trial were censored at the date of last participation in the trial. Testing was done at one-sided alpha of 0.1, first for the 25-mg dose and then, if significant, for the 10-mg dose. Sensitivity, supplementary, and subgroup analyses are discussed in Section 15 with results in Section 16.

6.2.3.4. Results of Analyses, Study 201

Patient Enrollment and Disposition

The study screened a total of 416 subjects for Study 201 amongst which 256 were randomized and were considered the ITT population. Of these, 196 subjects who received study treatment and completed the study without major deviations were defined as the per protocol (PP) population and used for supportive analyses of the primary endpoint. The safety population included 255 subjects who had received at least one dose of study drug by the actual treatment received. The subject enrollment and disposition for Study 201 are reviewed in Table 17.

Table 17. Patient Disposition, Study 201

Disposition	Brensocatib 10 mg N=82	Brensocatib 25 mg N=87	Placebo N=87	Total N=256
Screened				416
Screen failure				160
Randomized	82 (100)	87 (100)	87 (100)	256 (100)
Analysis set				
Intent-to-treat (ITT)	82 (100)	87 (100)	87 (100)	256 (100)
Per-protocol (PP)	65 (79.3)	67 (77.0)	64 (73.6)	196 (76.6)
Safety[1]	81 (98.8)	89 (102.3)	85 (97.7)	255 (99.6)
Completed study	76 (92.7)	75 (86.2)	74 (85.1)	225 (87.9)
Study discontinuation reason				
Adverse event	3 (3.7)	3 (3.4)	2 (2.3)	8 (3.1)
Death	0	1 (1.1)	0	1 (<1)
Lost to follow-up	1 (1.2)	0	0	1 (<1)
Non-compliance with study drug	0	1 (1.1)	0	1 (<1)
Physician decision	0	1 (1.1)	1 (1.1)	2 (<1)
Withdrawal by subject	2 (2.4)	4 (4.6)	10 (11.5)	16 (6.2)
Other	0	2 (2.3)	0	2 (<1)
Completed treatment	71 (86.6)	73 (83.9)	67 (77.0)	211 (82.4)
Treatment discontinuation reason				
Adverse event	6 (7.3)	6 (6.9)	6 (6.9)	18 (7.0)
Death	0	1 (1.1)	0	1 (<1)
Non-compliance with study drug	1 (1.2)	0	0	1 (<1)
Physician decision	1 (1.2)	1 (1.1)	2 (2.3)	4 (1.6)
Protocol violation	1 (1.2)	0	0	1 (<1)
Withdrawal by subject	2 (2.4)	6 (6.9)	11 (12.6)	19 (7.4)
Other	0	0	1 (1.1)	1 (<1)

Source: Clinical Study Report Table 7 and Table 8 (Pages 58-59, 61); findings reproduced by statistical reviewer using adsl.xpt;
[1] Treatment arm for the safety population is based on the actual treatment received rather than the randomized treatment arm. The actual treatment for one subject randomized to brensocatib 10 mg and one subject randomized to placebo was brensocatib 25 mg. One subject was randomized to placebo but did not receive any doses of study drug.
All values expressed as n(%) unless stated otherwise. Percentages out of N.
Abbreviations: ITT, intent-to-treat, N, number of subjects randomized, PP, per-protocol, QD, once daily

Most subjects (225 subjects, 87.9%) completed the study with numerically fewer subjects (6 subjects, 7.3%) in the brensocatib 10-mg group discontinuing the study relative to the brensocatib 25-mg and placebo groups (12 subjects, 13.8% and 13 subjects, 14.9%, respectively). The most common reason for study discontinuation in the placebo group was "subject withdrew consent" while the treatment groups demonstrated greater variability ranging from subject withdrawal of consent, adverse events, and death (Table 17). Forty-five (17.6%)

subjects discontinued treatment with numerically higher proportion of subjects discontinuing treatment from the placebo group (20 subjects, 23.0%) compared to either the 10 mg or 25 mg brensocatib groups (11 subjects, 13.4% and 14 subjects, 16.1%, respectively). As with study discontinuation, the most common reason for treatment discontinuation was subject decision to withdraw from study treatment followed by adverse events and physician decision. The small differences in treatment discontinuation and study withdrawal are unlikely to have substantial impacts on the interpretation of the safety or efficacy results.

Subject Demographics

The baseline demographics for Study 201 are summarized in Table 18. Overall, the population had a mean age of 64.1 years (range 22 to 84 years), and the majority were female (68.0%), white (87.9%), and never smokers (66.4%). There were no significant imbalances between treatment groups in baseline demographics.

Table 18. Baseline Demographics and Clinical Characteristics, ITT Population, Study 201

Demographics/ Characteristics	Brensocatib 10 mg N=82	Brensocatib 25 mg N=87	Placebo N=87	Total N=256
Age				
Mean (SD)	64.6 (12.4)	63.7 (12.7)	64.0 (11.9)	64.1 (12.3)
Median	67.5	66	67	66
IQR	57, 74	59, 72	59, 73	59, 73
Min, max	26, 83	22, 80	31, 84	22, 84
Age group, n(%)				
<65 Years	34 (41.5)	39 (44.8)	33 (37.9)	106 (41.4)
≥65 Years	48 (58.5)	48 (55.2)	54 (62.1)	150 (58.6)
Sex, n(%)				
Female	57 (69.5)	62 (71.3)	55 (63.2)	174 (68.0)
Male	25 (30.5)	25 (28.7)	32 (36.8)	82 (32.0)
Race, n(%)				
African American/black people of African origin	0	2 (2.3)	2 (2.3)	4 (1.6)
Asian	5 (6.1)	5 (5.7)	13 (14.9)	23 (9.0)
Caucasian (white)	76 (92.7)	78 (89.7)	71 (81.6)	225 (87.9)
Native Hawaiian or other Pacific Islander	1 (1.2)	1 (1.1)	1 (1.1)	3 (1.2)
Other	0	1 (1.1)	0	1 (<1)
Ethnicity, n(%)				
Hispanic or Latino	2 (2.4)	4 (4.6)	0	6 (2.3)
Not Hispanic or Latino	80 (97.6)	83 (95.4)	87 (100.0)	250 (97.7)
Geographical region, n(%)				
Asia-Pacific	28 (34.1)	33 (37.9)	34 (39.1)	95 (37.1)
Eastern Europe (Bulgaria/Poland)	11 (13.4)	11 (12.6)	12 (13.8)	34 (13.3)
Europe	22 (26.8)	18 (20.7)	20 (23.0)	60 (23.4)
North America	21 (25.6)	25 (28.7)	21 (24.1)	67 (26.2)
BSI score, n(%)				
≤4	18 (22.0)	18 (20.7)	17 (19.5)	53 (20.7)
5-8	27 (32.9)	26 (29.9)	36 (41.4)	89 (34.8)
≥9	37 (45.1)	43 (49.4)	34 (39.1)	114 (44.5)

Demographics/ Characteristics	Brensocatib 10 mg N=82	Brensocatib 25 mg N=87	Placebo N=87	Total N=256
Number of PExs in previous 12 months, n(%)				
0-2	59 (72.0)	51 (58.6)	61 (70.1)	171 (66.8)
3 or more	23 (28.0)	36 (41.4)	25 (28.7)	84 (32.8)
Maintenance use of macrolides at baseline[a], n(%)	13 (15.9)	16 (18.4)	15 (17.2)	44 (17.2)
Pa colonization at baseline[a], n(%)				
Negative	54 (65.9)	54 (62.1)	57 (65.5)	165 (64.5)
Positive	28 (34.1)	33 (37.9)	30 (34.5)	91 (35.5)
Baseline FEV1% predicted post-bronchodilator, n(%)				
<50%	23 (28.0)	18 (20.7)	24 (27.6)	65 (25.4)
≥50%	59 (72.0)	69 (79.3)	61 (70.1)	189 (73.8)
History of asthma, n(%)	18 (22.0)	21 (24.1)	25 (28.7)	64 (25.0)
History of COPD, n(%)	12 (14.6)	13 (14.9)	17 (19.5)	42 (16.4)
Use of inhaled steroids, n(%)	43 (52.4)	49 (56.3)	52 (59.8)	144 (56.2)
Hospitalized in prior 2 years, n(%)	31 (37.8)	31 (35.6)	30 (34.5)	92 (35.9)

Source: Clinical Study Report Table 9 and Table 10 (Pages 62-63, 64-65); findings reproduced by statistical reviewer using adsl.xpt;
[a] Maintenance use of macrolides and *Pa* colonization at baseline are based on as-randomized baseline strata variables.
Abbreviations: BSI, bronchiectasis severity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; IQR, interquartile range, ITT, intent-to-treat, max, maximum; min, minimum; N, number of subjects; n, number of subjects within specific demographic or with specific characteristic; Pa, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation; SD, standard deviation

The overall baseline NCFB characteristics (Table 18) were balanced between the treatment groups and generally represented the heterogeneity of disease features and severity that is characteristic of NCFB. The overall population had a mean post-bronchodilator FEV1 of 67.8% predicted (range 20 to 135) and a mean BSI score of 8.3 (range 0 to 21) with the majority of patients having moderate (34.8%) to severe disease (44.5%). The majority of subjects (66.8%) had ≤2 PEx in the preceding 12 months prior to enrollment and were negative for *P. aeruginosa* (64.5%). Half the population was using inhaled steroids (56.3%) while chronic macrolide use was uncommon (17.2%). COPD and asthma history, documented for the assessment of the exclusion criteria (refer to Section 6.2.3.2), were secondary diagnoses in 16.4% and 25.0% of subjects, respectively. Underlying bronchiectasis etiology was not documented for subjects in Study 201; however, review of the medical history data demonstrates that most subjects had an underlying history of recurrent or chronic infections from early childhood or were reported to have bronchiectasis for unknown or "idiopathic" reasons.

Analysis of Efficacy-Primary Endpoint

As summarized in Table 19, the number of subjects who experienced a pulmonary exacerbation in the placebo group was 42 (48.3%), higher compared to 26 (31.7%) in the brensocatib 10-mg group and 29 (33.3%) in the brensocatib 25-mg group. The median time to first PEx was 189 days in the placebo group and was not estimable for either brensocatib group because of low numbers of observed events. The one-sided p-values for the stratified log-rank test were 0.01 and

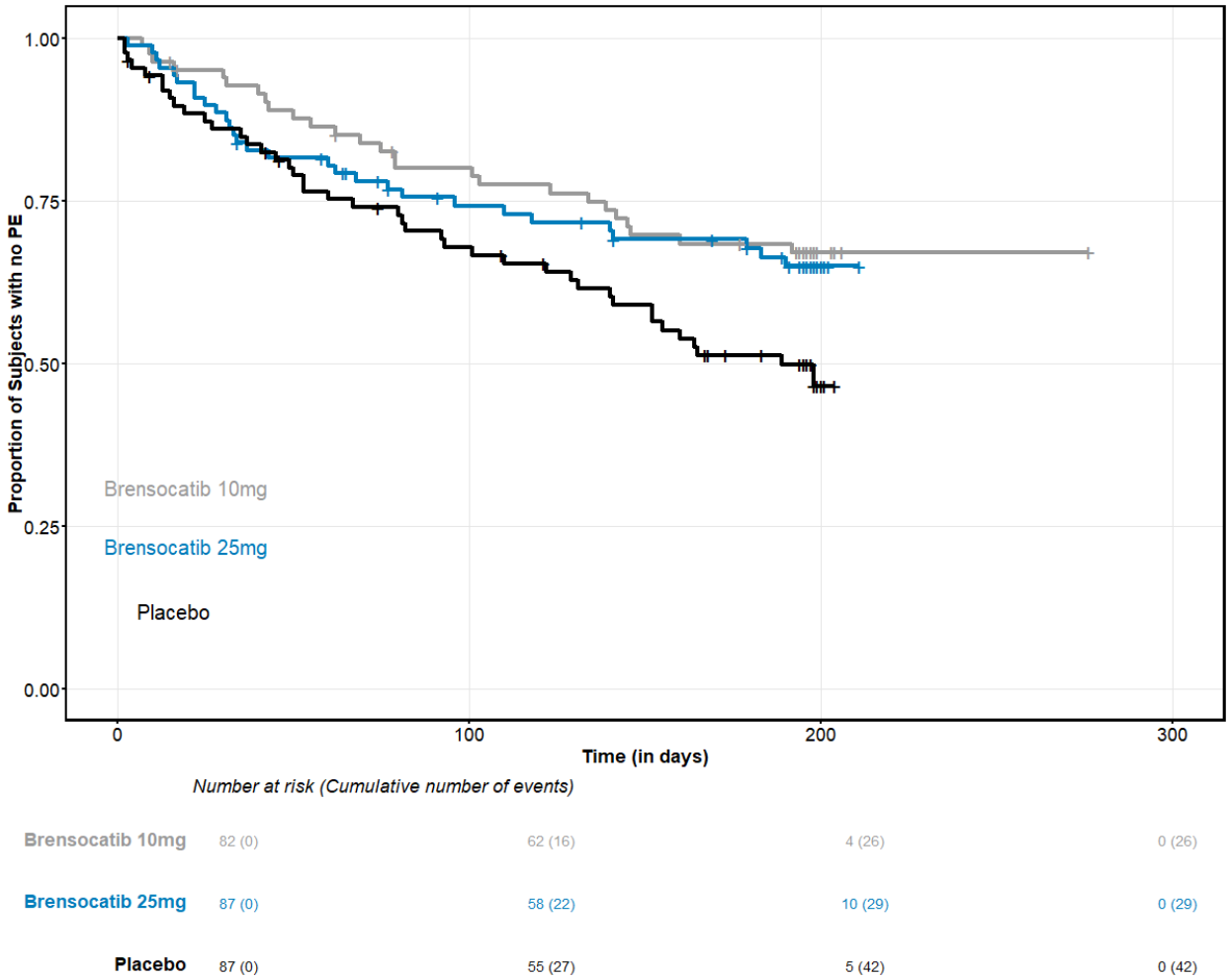
0.02 compared to placebo for the brensocatib 10-mg and 25-mg groups, respectively. Both brensocatib groups demonstrated statistically significant and clinically meaningful reductions in time to first pulmonary exacerbation through Week 24 compared to placebo, with p-values well below the prespecified one-sided alpha of 0.1. Figure 2 displays the Kaplan Meier plot of time to first pulmonary exacerbation in days over the 24-week treatment period.

Table 19. Primary Analysis: Time to First Pulmonary Exacerbation Through Week 24 in ITT Analysis Set, Study 201

Parameter	Brensocatib 10 mg N=82	Brensocatib 25 mg N=87	Placebo N=87
Subjects with PEx, n(%)	26 (31.7)	29 (33.3)	42 (48.3)
Median time to first PEx in days[1] (95% CI)	NE (NE, NE)	NE (NE, NE)	189 (140, NE)
One-sided p-value[2]	0.01	0.02	-

Source: Clinical Study Report Table 12 (Page 68); findings reproduced by the statistical reviewer using adtte.xpt
[1] Kaplan Meier estimates were used for the median time to first PEx. Confidence intervals are two-sided 95% confidence intervals.
[2] The stratified log-rank test was used to estimate a one-sided p-value, stratified by sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit and maintenance antibiotic use at baseline.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, not estimable; PEx, pulmonary exacerbation

Figure 2. Kaplan Meier Plot of Time to First Pulmonary Exacerbation Over 24-Week Treatment Period in ITT Analysis Set, Study 201



Source: Clinical Study Report Figure 2 (Page 69); findings reproduced by the statistical reviewer using adtte.xpt
Abbreviations: ITT, intent-to-treat, PE, pulmonary exacerbation

The review team was able to replicate the Applicant's analyses of the primary endpoint, and the results demonstrate statistically persuasive superiority of both brensocatib groups compared to placebo in Study 201. Although Study 201 is limited by both a smaller enrolled population and shorter treatment duration, the primary endpoint results are consistent with those obtained from Study 301 and support the overall demonstration of the treatment effect of brensocatib. Results for key secondary endpoints are discussed in Section 16.

6.3. Key Efficacy Review Issues

6.3.1. Dose Selection

Issue

The Applicant submitted data from two clinical trials evaluating the efficacy and safety of brensocatib 10 mg and 25 mg versus placebo. The data demonstrate that both doses met the

primary endpoints of both trials, as well as several key secondary endpoints, with minimal or no difference in the magnitude of the treatment effects. The Applicant initially proposed marketing only the 25-mg dose based on two findings from Study 301: that a statistically significant increase in post-BD FEV1 was achieved for the 25-mg arm only compared to placebo and that a nominal improvement in the QoL-B RSS supported 25 mg as the optimal dose. The review team questioned whether these data were persuasive enough, together with the safety profile of each dose, to support marketing only the 25-mg dose.

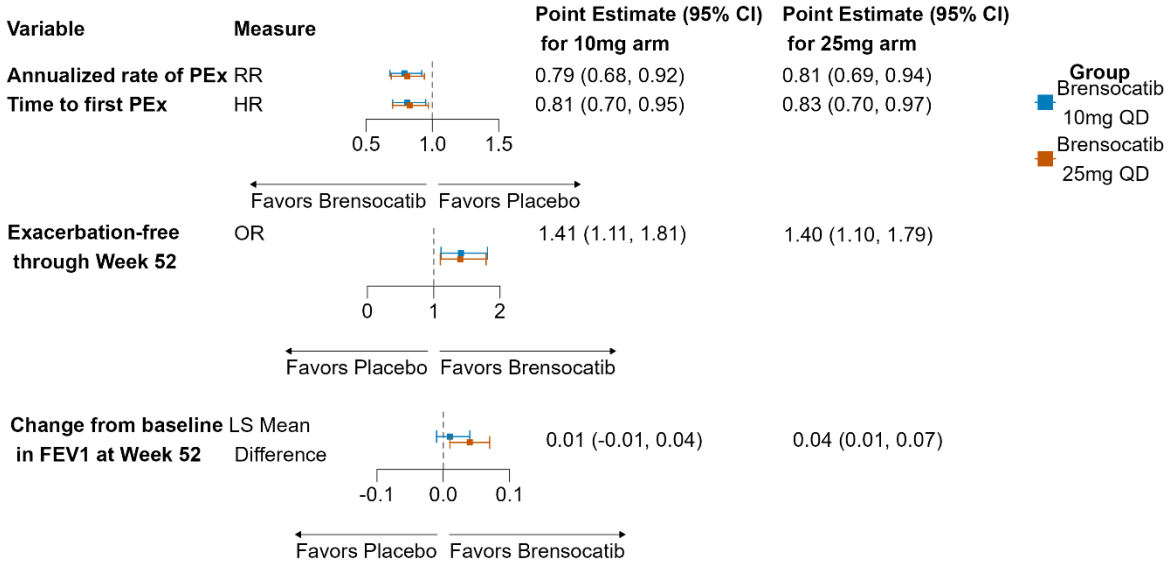
Background

The Applicant selected two doses, 10 mg and 25 mg, for evaluation in Studies 301 and 201 based on PD and safety data from a phase 1 study (D6190C00001) in healthy subjects as well as simulation data. Refer to Section 6.1 for further details on the selection of these doses for pivotal trials.

In Study 201, the primary endpoint of time to first PEx was statistically significant for both brensocatib doses compared to placebo. The separation of survival curves for the brensocatib treatment groups compared to placebo are shown in Figure 2. The stratified log-rank test p-values and survival curves were similar between doses (10 mg: 0.01, 25 mg: 0.02).

Figure 3 summarizes the results of the primary and first three key secondary endpoints in Study 301, with full results in Section 6.2.2.4. The primary endpoint, annualized rate of PEx, and first two key secondary endpoints, time to first PEx and responder status for exacerbation-free through Week 52, were statistically significant with similar point estimates and confidence intervals for both doses. The next secondary endpoint in the testing hierarchy was change from baseline in post-BD FEV1 in liters at Week 52; statistical significance was achieved compared to placebo for the brensocatib 25-mg group, but not for the brensocatib 10-mg group.

Figure 3. Efficacy Analysis: Forest Plot of the Primary and Three Key Secondary Endpoints Comparing Brensocatib and Placebo in ITT Analysis Set, Study 301



Source: Summary of findings reproduced by the statistical reviewer using adces.xpt, adre.xpt, adtte.xpt; detailed results shown in Table 10, Table 11, Table 12, and Table 13.
Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; HR, hazard ratio; ITT, intent-to-treat; LS, least squares; OR, odds ratio; PEx, pulmonary exacerbation; QD, once daily; RR, rate ratio

Assessment

Evaluation of Treatment Effect

Since both doses met the primary endpoints of Studies 201 and 301, as well as several key secondary endpoints of Study 301, we performed additional analyses to explore whether specific subgroups defined by baseline demographic and disease characteristics, such as underlying NCFB etiology (see Sections 6.2.2.4 and 6.2.3.4), revealed meaningful differences in the treatment effects by brensocatib dose.

The Forest plot of the subgroup analyses of the primary endpoint of annualized rate of PEx through Week 52 in Study 301 is given in Table 16, with results across subgroups consistent with the overall population results. We also performed post-hoc subgroup analyses by etiology, which are presented in Figure 68. Meaningful differences in treatment effects by brensocatib dose were not identified within these subgroups.

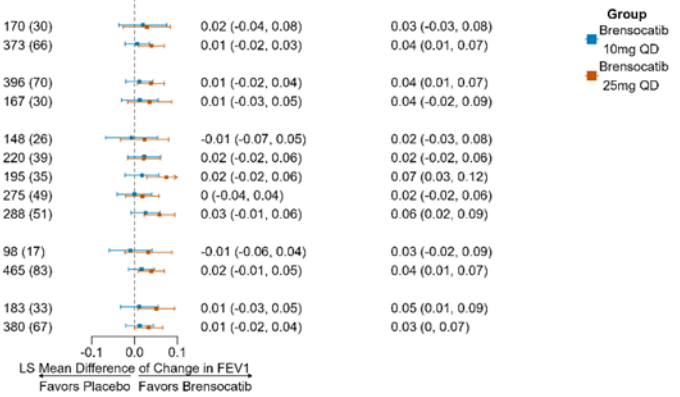
Although a statistically significant result was achieved for the key secondary endpoint of change from baseline in post-BD FEV1 at Week 52 compared to placebo for brensocatib 25 mg, but not for brensocatib 10 mg, the review team did not find the numeric differences to be clinically meaningful. American Thoracic Society (ATS) guidelines have a repeatability parameter in the criteria for determining an acceptable FEV1 measurement at any given assessment timepoint. That repeatability criterion allows for a difference of up to 150 mL between the two largest measurements (Graham et al. 2019). Furthermore, studies evaluating the within-patient variability from visit-to-visit in spirometry measurements have found up to 200 mL difference between assessments in healthy subjects and patients with respiratory diseases (Jensen et al. 2007; Dean et al. 2018). The least squares mean for the brensocatib 25-mg group was quite small at 0.038 L or 38 mL, well within the documented repeatability range and between-visit range of

variability for FEV1 measurement. In addition, separation between the two doses was not observed until Week 52 measurements. We also note that some literature suggests FEV1 may have limitations in its prognostic value in bronchiectasis, compared to other measures of lung function (e.g., residual volume and diffusion capacity) or non-lung function parameters (e.g., frequency of PEx) (Radovanovic et al. 2018). Therefore, taken together, the clinical meaningfulness of this result is unclear, as the review team also acknowledges that statistical significance was achieved for the mean measurement of this outcome with high intra-patient variability.

We, therefore, considered further analysis of this endpoint relevant to the issue of dose selection. The review team performed a post-hoc comparison of brensocatib 25 mg and 10 mg for change from baseline in post-BD FEV1 (L) at Week 52 in Study 301. The estimated least squares mean difference between brensocatib 25 mg and brensocatib 10 mg was small: 0.026 or 26 mL (95% CI = −0.0003, 0.053) with a nominal p-value of 0.052. Further, subgroup analyses were prespecified by the Applicant for the same subgroups as for the primary endpoint. The results from a selection of these subgroups pertinent to dose selection are presented in Figure 4.

Figure 4. Subgroup Analysis: Forest Plot of the Least Squares Mean Differences of Change From Baseline in FEV1 (L) at Week 52 Between Brensocatib and Placebo in ITT Analysis Set, Study 301

Variable	Brensocatib 10mg QD, n (%)	Brensocatib 25mg QD, n (%)	Placebo, n (%)	LS Mean Difference (95% CI) for 10mg arm	LS Mean Difference (95% CI) for 25mg arm
Overall	583 (100)	575 (100)	563 (100)	0.01 (-0.01, 0.04)	0.04 (0.01, 0.06)
Age Group					
12 To <18 Years	17 (3)	16 (3)	8 (1)	0.29 (-0.13, 0.71)	0.32 (-0.1, 0.74)
18 To <65 Years	289 (50)	257 (45)	295 (52)	0 (-0.04, 0.03)	0.03 (-0.01, 0.07)
>=65 Years	277 (48)	302 (53)	260 (46)	0.02 (-0.01, 0.05)	0.04 (0.01, 0.08)
<75 Years	500 (86)	491 (85)	470 (83)	0.01 (-0.02, 0.04)	0.04 (0.01, 0.07)
>=75 Years	83 (14)	84 (15)	93 (17)	0.02 (-0.03, 0.08)	0.03 (-0.03, 0.08)
Adult	566 (97)	559 (97)	555 (99)	0.01 (-0.02, 0.03)	0.04 (0.01, 0.06)
Sex					
Female	385 (66)	360 (63)	362 (64)	0 (-0.03, 0.03)	0.03 (0, 0.06)
Male	198 (34)	215 (37)	201 (36)	0.04 (-0.01, 0.09)	0.05 (0, 0.1)
Race					
Asian	63 (11)	64 (11)	64 (11)	0.02 (-0.03, 0.06)	0.07 (0.02, 0.11)
Other	15 (3)	13 (2)	11 (2)	0.03 (-0.12, 0.18)	0.15 (-0.1, 0.4)
White	431 (74)	430 (75)	405 (72)	0.01 (-0.02, 0.04)	0.03 (0, 0.06)
Ethnicity					
Hispanic Or Latino	177 (30)	164 (29)	170 (30)	0.02 (-0.04, 0.08)	0.03 (-0.03, 0.08)
Not Hispanic Or Latino	391 (67)	397 (69)	373 (66)	0.01 (-0.02, 0.03)	0.04 (0.01, 0.07)
Number of PEs in prior 12 months					
<3	411 (70)	412 (72)	396 (70)	0.01 (-0.02, 0.04)	0.04 (0.01, 0.07)
>=3	172 (30)	163 (28)	167 (30)	0.01 (-0.03, 0.05)	0.04 (-0.02, 0.09)
Pooled BSI Group					
4 Or Less	136 (23)	150 (26)	148 (26)	-0.01 (-0.07, 0.05)	0.02 (-0.03, 0.08)
5-8	275 (47)	239 (42)	220 (39)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)
9 Or More	168 (29)	182 (32)	195 (35)	0.02 (-0.02, 0.06)	0.07 (0.03, 0.12)
<Median	286 (49)	278 (48)	275 (49)	0 (-0.04, 0.04)	0.02 (-0.02, 0.06)
>=Median	293 (50)	293 (51)	288 (51)	0.03 (-0.01, 0.06)	0.06 (0.02, 0.09)
Baseline FEV1 % predicted post-bronchodilator					
<50%	101 (17)	102 (18)	98 (17)	-0.01 (-0.06, 0.04)	0.03 (-0.02, 0.09)
>=50%	478 (82)	469 (82)	465 (83)	0.02 (-0.01, 0.05)	0.04 (0.01, 0.07)
Smoking status					
Former Smoker	164 (28)	163 (28)	183 (33)	0.01 (-0.03, 0.05)	0.05 (0.01, 0.09)
Never Smoked	419 (72)	412 (72)	380 (67)	0.01 (-0.02, 0.04)	0.03 (0, 0.07)



Source: Clinical Study Report Tables, Figures, and Data Listings, Table 16.2.7.2-3 g (Pages 249-263); findings reproduced by the statistical reviewer using adtte.xpt
Abbreviations: BSI, bronchiectasis severity index; FEV1, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least squares; PEx, pulmonary exacerbation; QD, once daily

The subgroup analysis results were consistent with the analysis of the overall population. Any differences in the observed least squares mean between brensocatib doses for individual subgroups were generally small, consistent with the overall population difference, and not clinically meaningful. Ultimately, the review team concluded that the post-BD FEV1 results on their own were not persuasive enough to preclude approval of the 10-mg dose. Additional

analyses did not identify a particular subgroup of patients who demonstrated a more robust response on FEV1 to either dose.

Initial justification for the 25-mg dose also relied on the observation of a nominal improvement in patient symptoms as captured by the QoL-B RSS, for which the greatest increase was seen in the 25-mg treatment group (Table 15). This improvement did not reach statistical significance. Furthermore, evaluation of clinically meaningful change by both Agency-determined and Applicant-determined clinically meaningful change threshold range did not reveal clinically meaningful improvements in the QoL-B RSS with either dose. As a result, the nominal improvement in QoL-B RSS difference observed between the 10 mg and 25-mg doses is insufficient to exclude the option of the 10-mg dose. Further discussion of the analyses investigating the clinical meaningfulness of the observed treatment effect on the QoL-B RSS endpoint is presented in Section 6.3.3.

Evaluation of Safety

Safety results are presented in detail in Section 7. Analysis of safety data from Study 301 and Study 201 demonstrates both the 10 mg and 25-mg doses have generally comparable safety profiles, although some dose-dependent (10 mg <25 mg) effects were observed among a limited number of adverse reactions, such as upper respiratory tract infection, headache, and skin-related events (e.g., rash, dry skin, hyperkeratosis). Since both doses appear to be equally efficacious, the review team performed additional analyses to characterize better these signals and to explore whether one dose appeared to have a more favorable benefit-risk profile for specific subgroups.

Analyses by sex, race, history of smoking, underlying bronchiectasis etiology, baseline NCFB characteristics, and concomitant medications did not reveal meaningful trends to suggest any of these factors could be suitable predictors of tolerability or increased risk with either dose. The results of these analyses are presented in detail in Section 7.7.1. No clinically meaningful differences between the two brensocatib doses were observed in the frequency of subjects who discontinued treatment due to an AE (Sections 7.6.1.1 and 7.6.2.1).

Overall, review of the safety data from Studies 301 and 201 reveals dose-dependent adverse reactions that support marketing of the 10-mg dose as an option for those patients who may experience tolerability issues.

Evaluation of Pharmacokinetics

The Applicant performed exposure-response analysis using data from Studies 201 and 301 to support the proposed 25 mg QD dose. Based on endpoints of annualized rate of PEx and time to first PEx, the Applicant claimed that subjects with steady state brensocatib area under the concentration-time curve $(AUC)_{tau}$ higher than 1100 ng*h/mL had statistically significant improvements in both endpoints relative to subjects with AUC_{tau} less than 1100 ng*h/mL. In addition, the Applicant also claimed that subjects with steady state brensocatib AUC_{tau} greater than 1531 ng*h/mL showed minimal variation in the change from baseline in post-BD FEV1 as compared to subjects with AUC_{tau} less than 1531 ng*h/mL. Based on the predicted brensocatib exposure in Study 301, the proportion of subjects with AUC_{tau} greater than 1100 ng*h/mL was approximately 69% and 100% in the 10-mg and 25-mg dose groups, respectively. The proportion of subjects with AUC_{tau} greater than 1531 ng*h/mL was approximately 45% and 99% in the 10-mg and 25-mg dose groups, respectively.

Notably, the results from exposure-response analysis based on annualized rate of PEx and time to first PEx are inconsistent with the observed efficacy results from Study 301, in which a similar rate ratio compared to placebo was demonstrated for both brensocatib dose groups for the annualized rate of PEx. The reason for this discrepancy between the observed efficacy results and exposure-response analyses may be because PK data from Study 301 were not available in approximately half the enrolled subjects, a function of the protocol-specified PK collection. In addition, the difference in post-BD FEV1 at Week 52 between subjects with brensocatib AUC_{tau} >1531 ng*h/mL relative to subjects with AUC_{tau} <1531 ng*h/mL is approximately 40 mL (visually estimated from Figure 14, Module 2.7.2, Summary of Clinical Pharmacology). This magnitude difference in FEV1 is not considered to be clinically meaningful (refer to discussion in Section 6.2.2.4) and, therefore, does not provide compelling evidence for selection of the 25-mg dose over the 10-mg dose.

Overall, as PK data are not available for approximately half the subjects enrolled in Study 301, the interpretation of the exposure-response efficacy analysis is limited.

Conclusion

Review of the efficacy and PK data from Studies 301 and 201 supports comparable efficacy for both the 10-mg and 25-mg doses. Both doses met the primary endpoints and several key secondary endpoints with minimal or no difference in the treatment effects. The Applicant initially proposed marketing only the 25-mg dose; however, the review team found the justification for this approach to be insufficient. The size of the treatment effect for both doses compared to placebo in post-BD FEV1, as well as the difference between doses, were too small to be clinically meaningful, and neither dose demonstrated a clinically meaningful change in the QoL-B RSS. Additional analyses to characterize the benefit-risk profile of each dose revealed several key findings: the absence of demographic or disease-related predictors for greater benefit with a specific dose; the occurrence of some dose-dependent adverse reactions, and significant limitations to the PK data to support a clear exposure-response relationship. Therefore, in discussion with the Applicant, the recommendation is to market both doses, thus allowing patients unable to tolerate 25 mg to gain benefit from 10 mg. Although the Agency usually recommends marketing the lowest effective dose, the observed difference in post-BD FEV1 suggests that some patients, who can tolerate 25 mg, may benefit from additional improvement in lung function (although the clinical meaning of such difference remains unclear). The availability of both doses as options will allow for shared decision making at the prescriber patient level. See Section 23 for discussion of inclusion of both doses in the USPI.

6.3.2. Efficacy in Adolescents

Issue

The Applicant enrolled 41 adolescent subjects aged 12 to <18 years in Study 301, as specified in the amended agreed pediatric study plan dated May 16, 2022. The Applicant reports that both doses of brensocatib demonstrated a positive trend in the reduction in the annualized rate of PEx compared to placebo as well as an increase in time to first PEx in the adolescent subgroup, consistent with the effect in the overall study population in Study 301. Similar trends were observed for responder status for being exacerbation-free and change from baseline in post-BD FEV1. Based on these results, the Applicant proposed marketing of brensocatib in patients 12

years of age and older with NCFB. The review team identified some limitations to the adolescent data and investigated whether there was sufficient evidence to support a favorable benefit-risk for brensocatib in adolescents.

Background

The burden of NCFB in children (younger children and adolescents) is difficult to ascertain because of delays in diagnosis related to many factors including sociodemographic determinants that affect access to healthcare, physician awareness of NCFB presentation in the pediatric population, and the availability of high-resolution CT scans updated with pediatric protocols (Goyal et al. 2016). As a result, the few studies aiming to define the NCFB prevalence among children are strikingly variable depending on the surveyed population with reported prevalences ranging from 0.2 to 735 cases per 100,000 children (Goyal et al. 2016; Chang et al. 2018).

As with adults, children with NCFB display substantial heterogeneity in the underlying etiologies that lead to bronchiectasis. Although the etiologies are generally similar between adult and pediatric populations, there are differences in their frequencies. Infection is the most common etiology for all patients with NCFB regardless of age. Among children, the next most common etiologies are primary immunodeficiency, aspiration, ciliary abnormalities, and congenital malformations. In contrast, COPD, connective tissue disorder, immunodeficiency, and asthma complete the top five most common etiologies for adults (Brower et al. 2014; Lonni et al. 2015; Goyal et al. 2016).

There are few studies aiming to define the pathophysiology of NCFB in the pediatric population relative to adults. Analysis of BAL fluid from pediatric NCFB patients demonstrate airway neutrophilia similar to adult BAL fluid analyses (Kapur et al. 2012). However, children display differences in the composition of the airway microbiota (Kapur et al. 2012; van der Gast et al. 2014) with the most prevalent bacterial pathogen being *Hemophilus influenza* (versus *P. aeruginosa*) (Pizzutto et al. 2015). These differences may have implications for understanding the aberrant immunological responses leading to airway epithelial tissue injury and entry into the bronchiectasis cycle among pediatric patients.

Although there is some limited evidence to suggest differences in underlying etiology and initial development of bronchiectasis between adults and children, the pathogenesis and clinical course of established bronchiectasis are more clearly characterized (Chang et al. 2021a; Chang et al. 2021b). Children with NCFB share common clinical features with adults, such as a wet, productive cough and recurrent exacerbations of lower airway infection necessitating treatment with antibiotics. For both children and adults, frequent exacerbations lead to a cycle of unchecked airway inflammation, driving airway tissue damage that worsens bronchiectasis and promotes further exacerbations. The management of established bronchiectasis in adult and pediatric patients also relies on the same fundamentals: maximizing airway mucociliary clearance and treatment and prevention of infections through acute and chronic oral and inhaled antibiotics, as well as inhaled corticosteroids and supplemental oxygen for more severe disease.

In summary, pediatric and adult patients with NCFB display a mixture of similarities and differences in airway microbiota and underlying etiology of bronchiectasis; however, regardless of age, once a patient has established bronchiectasis, the pathogenesis of disease progression follows the same progressive and cyclical course.

Assessment

Evaluation of Treatment Effect

Study 301 enrolled a total of 41 adolescent subjects, and their disposition in Study 301 is displayed in Table 20. The number of subjects with data available at Week 52 was 18 out of the 41 adolescents in the ITT analysis set. At the time of primary database lock, 16 adolescents had completed the study, 20 were still in the treatment period, and 3 had completed treatment and remained on study. Two subjects discontinued treatment and the study, one because of an AE (nausea) and one who withdrew consent.

Table 20. Disposition, Adolescents in ITT Population, Study 301

Disposition	Brensocatib 10 mg N=17	Brensocatib 25 mg N=16	Placebo N=8	Total N=41
Study completion				
No	0	2 (12.5)	0	2 (4.9)
Ongoing	11 (64.7)	8 (50.0)	4 (50.0)	23 (56.1)
Yes	6 (35.3)	6 (37.5)	4 (50.0)	16 (39.0)
Study discontinuation reason				
Adverse event	0	1 (6.2)	0	1 (2.4)
Withdrawal by subject	0	1 (6.2)	0	1 (2.4)
Treatment completion				
No	0	2 (12.5)	0	2 (4.9)
Ongoing	9 (52.9)	7 (43.8)	4 (50.0)	20 (48.8)
Yes	8 (47.1)	7 (43.8)	4 (50.0)	19 (46.3)
Treatment discontinuation reason				
Adverse event	0	1 (6.2)	0	1 (2.4)
Withdrawal by subject	0	1 (6.2)	0	1 (2.4)

Source: Statistical Reviewer Analysis; adsl.xpt;
All values expressed as n(%) unless stated otherwise. Percentages out of N.
Abbreviations: ITT = Intent-to-treat, N = number of subjects randomized,

Randomization of adolescents in Study 301 was not stratified according to the same criteria as adults (Section 6.2.2.1). A summary of the baseline disease characteristics is presented in Table 21. There were some differences in the baseline disease characteristics of subjects randomized to brensocatib 10 mg and brensocatib 25-mg arms. The 10-mg arm had a higher frequency of subjects with BSI scores ≥9, with 3 or more PEx in the last 12 months, who were hospitalized in the last 24 months and who were on baseline antibiotics or inhaled steroids. Together, these factors demonstrate that subjects in the 10-mg arm were more likely to have severe NCFB compared to subjects in the brensocatib 25 mg or placebo arms. However, the adolescents enrolled collectively were comparable to the adult population in terms of severity and disease characteristics.

Table 21. Baseline Characteristics of Adolescent in ITT Population, Study 301

Characteristic	Brensocatib 10 mg N=17	Brensocatib 25 mg N=16	Placebo N=8
BSI Score			
≤4	7 (41.2)	9 (56.2)	2 (25.0)
5-8	6 (35.3)	6 (37.5)	5 (62.5)
≥9	4 (23.5)	1 (6.2)	1 (12.5)
Number of PEx in last 12 months			
1	8 (47.1)	9 (56.2)	4 (50.0)
2	3 (17.6)	5 (31.2)	2 (25.0)
3	4 (23.5)	0	0
4 or more	2 (11.8)	2 (12.5)	2 (25.0)
Antibiotic use at baseline	7 (41.2)	4 (25.0)	4 (50.0)
Macrolide use at baseline	4 (23.5)	4 (25.0)	3 (37.5)
Pseudomonas colonization at baseline	4 (23.5)	3 (18.8)	2 (25.0)
Baseline post-BD ppFEV1			
≥50%	15 (88.2)	14 (87.5)	8 (100.0)
<50%	2 (11.8)	2 (12.5)	0
Baseline eosinophil count			
<300/mm3	16 (94.1)	12 (75.0)	7 (87.5)
≥300/mm3	1 (5.9)	4 (25.0)	1 (12.5)
History of asthma	2 (11.8)	2 (12.5)	1 (12.5)
Inhaled steroid use	12 (70.6)	10 (62.5)	4 (50.0)
Hospitalization in last 24 months	7 (41.2)	2 (12.5)	4 (50.0)

Source: Clinical reviewer, adsl.xpt
Abbreviations: BD, bronchodilator; BSI, bronchiectasis, severity index; ITT, Intent-to-treat; mg, milligram; mm, millimeter; N, number of subjects randomized; PEx, pulmonary exacerbation; pp, percent predicted; ppREV1, percent predicted forced expiratory volume

The point estimates for the adolescent subgroup analysis of annualized rate of PEx through Week 52 favor both brensocatib groups compared to placebo, as summarized in Table 20. After adjusting for sputum sample classification as positive or negative for *P. aeruginosa* at screening, the number of prior PEx (<3 or ≥3) in the previous 12 months, and stratification region, the estimated rate ratio of PEx compared to placebo was 0.41 (95% CI = 0.11, 1.58) for the brensocatib 10-mg group and 0.73 (95% CI = 0.20, 2.68) for the brensocatib 25-mg group. Both confidence intervals include the null value of one, likely related to the small sample sizes.

Table 22. Subgroup Analysis: Annualized Rate of Pulmonary Exacerbations Through Week 52 in Adolescents in ITT Analysis Set, Study 301

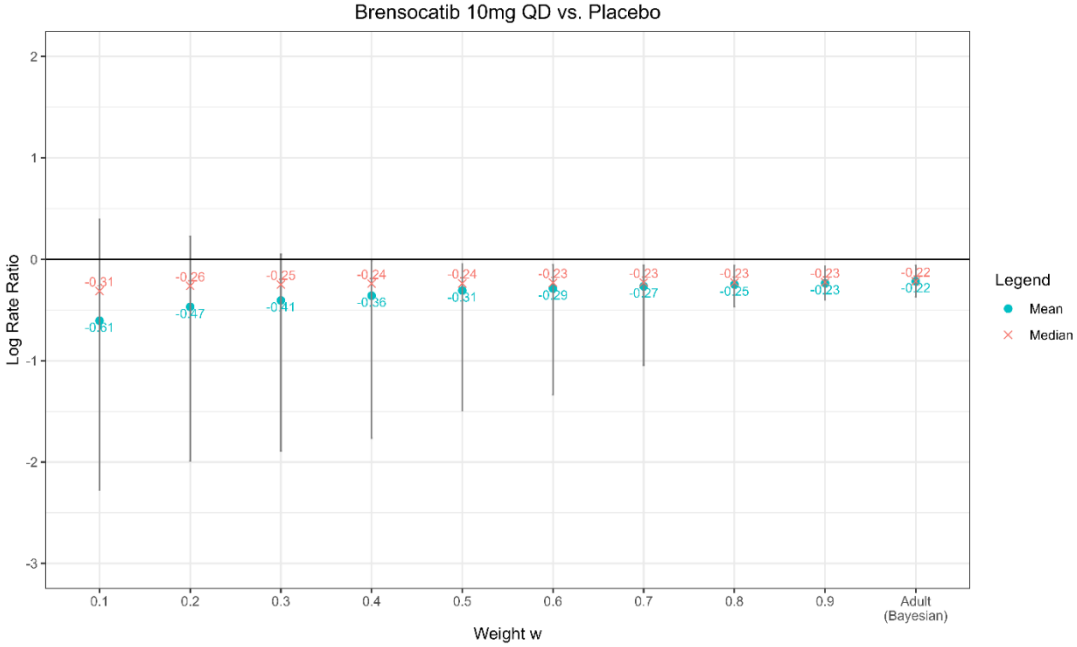
Parameter	Brensocatib 10 mg N=17	Brensocatib 25 mg N=16	Placebo N=8
Number of subjects with exacerbation events, n(%)			
0	11 (64.7)	10 (62.5)	3 (37.5)
1	3 (17.6)	4 (25.0)	1 (12.5)
2	3 (17.6)	0 (0)	4 (50.0)
≥3	0 (0)	2 (12.5)	0 (0)
Annualized rate of PExs[1] (95% CI)	0.35 (0.15, 0.86)	0.64 (0.28, 1.46)	0.87 (0.32, 2.35)

Parameter	Brensocatib 10 mg N=17	Brensocatib 25 mg N=16	Placebo N=8
Rate ratio compared to placebo[1] (95% CI)	0.41 (0.11, 1.58)	0.73 (0.20, 2.68)	-

Source: Clinical Study Report 16.2.7 Tables, Figures, and Data Listings, Table 16.2.7.1-3d (Page 25); findings reproduced by the statistical reviewer using adces.xpt
[1] The negative binomial regression model included treatment group, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, and stratification region (North America, Europe, Japan, and the Rest of the World) as covariates and the logarithm of time at risk in years as an offset variable.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, not estimable; PEx, pulmonary exacerbation; QD, once daily

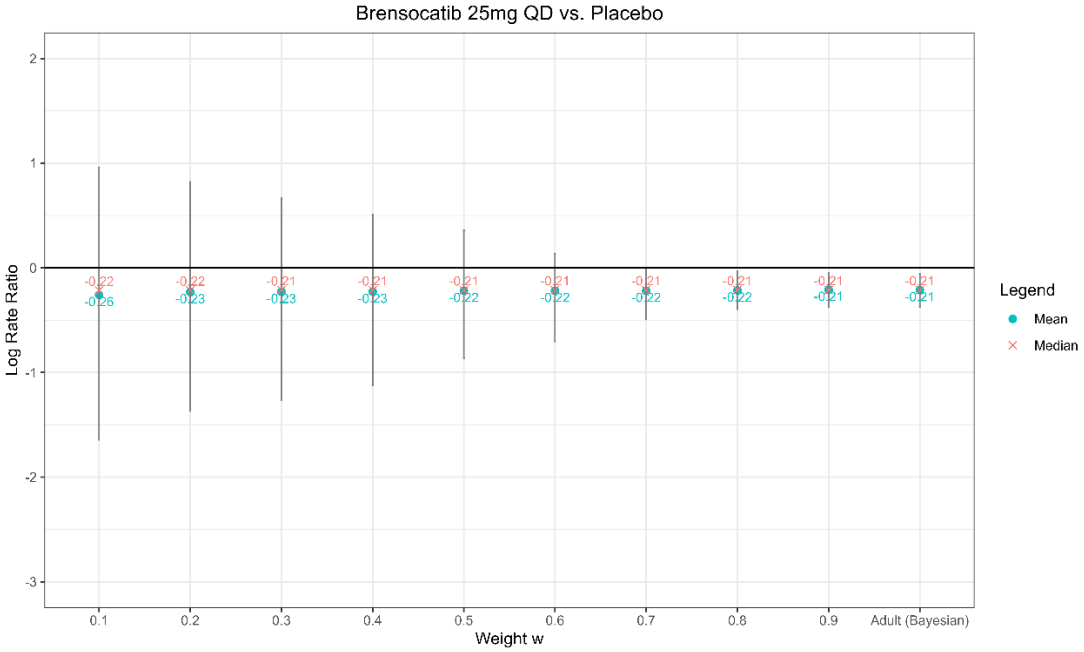
The Applicant prespecified an analysis for the primary endpoint for adolescents using negative binomial regression and a Bayesian hierarchical model. The prior distribution of the Bayesian approach was a mixture of a non-informative prior and a distribution of the treatment effects in adults, with the mixing weight ranging from 0 (no borrowing) to 1 (full borrowing) in increments of 0.1, performed for each dose separately. A detailed description of this analysis is in Section 15. The posterior mean and 95% credible intervals were calculated for each weight value. As shown in Figure 5 and Figure 6, 95% credible intervals exclude the null value of a log rate ratio of 0 for weights of 0.4 or higher for the brensocatib 10-mg group and weights of 0.8 or higher for the brensocatib 25-mg group, supporting the primary efficacy of both brensocatib doses in adolescents. Although the level of borrowing is lower for the brensocatib 10-mg group, this is not conclusive support for identifying the 10-mg dose as the only appropriate dose for adolescents given the small sizes of these subgroups.

Figure 5. Subgroup Analysis: Plot of Posterior Mean and 95% Credible Intervals of Log Rate Ratio Comparing Brensocatib 10 mg QD to Placebo From Bayesian Hierarchical Model for Adolescents in ITT Analysis Set, Study 301



Source: Clinical Study Report Figure 3 (Page 49); findings reproduced by the statistical reviewer using adces.xpt
Abbreviations: ITT, intent-to-treat; QD, once daily

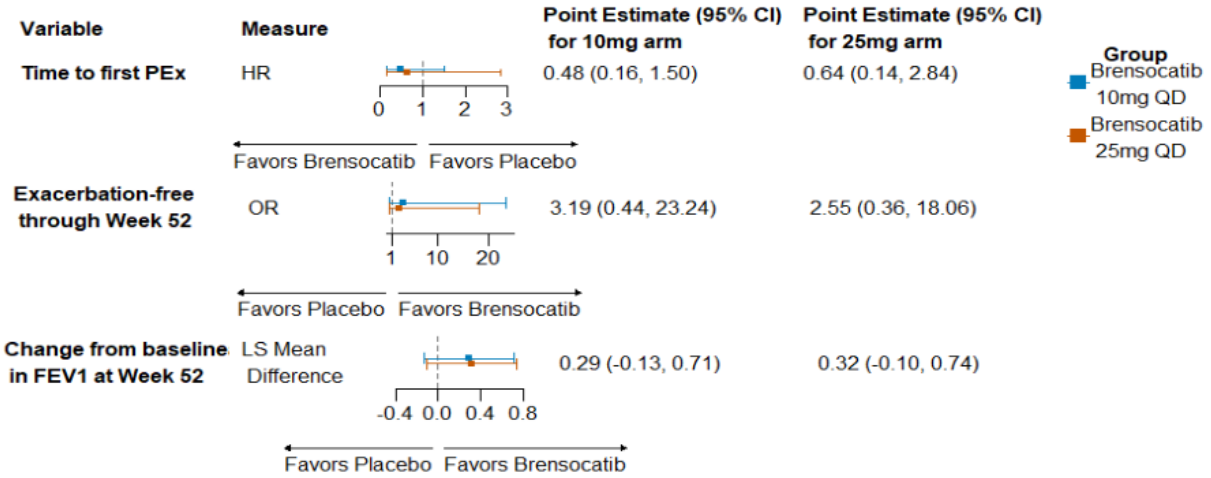
Figure 6. Subgroup Analysis: Plot of Posterior Mean and 95% Credible Intervals of Log Rate Ratio Comparing Brensocatib 25 mg QD to Placebo From Bayesian Hierarchical Model for Adolescents in ITT Analysis Set, Study 301



Source: Clinical Study Report Figure 3 (Page 49); findings reproduced by the statistical reviewer using adces.xpt
Abbreviations: ITT, intent-to-treat; QD, once daily

We also explored results for the key secondary endpoints for the adolescent subgroup. The point estimates and confidence intervals for the first three key secondary endpoints by frequentist analysis in the adolescent subgroup are presented in Figure 7. The number of severe PEx in adolescents was small (0, 1, and 2 in the brensocatib 10 mg, brensocatib 25 mg, and placebo groups, respectively) and so inferential between-group comparisons were not performed. The treatment effects for each of these key secondary endpoints favor both brensocatib doses compared to placebo.

Figure 7. Efficacy Analysis: Forest Plot of Three Key Secondary Endpoints Comparing Brensocatib and Placebo in Adolescents in the ITT Analysis Set, Study 301



Source: Summary of findings reproduced by the statistical reviewer using adces.xpt, adre.xpt, adtte.xpt
Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; HR, hazard ratio; ITT, intent-to-treat; LS, least squares; OR, odds ratio; PEx, pulmonary exacerbation; QD, once daily

The review team also noted that both point estimates for the change from baseline in post-BD FEV1 at Week 52 were larger for adolescents than in the overall population (10 mg: 0.01, 25 mg: 0.04, see Table 13). The review team analyzed this endpoint by age in the adolescent subgroup to investigate whether changes in FEV1 may be attributed to growth. A trend across age was not identified, which may be a result of the limited data available for analysis. The review team also investigated the change from baseline in percent predicted FEV1 at Week 52 to understand potential differences as a function of growth; however, the small sample size also limited this analysis. Overall, results for the adolescent subgroup were consistent with results for the whole population, and we did not identify any clinically significant trends by age within the adolescent subgroup.

Evaluation of Safety

The evaluation of safety for the 41 adolescents enrolled in Study 301 is described in detail in Sections 7.6.1.10 and 17. In general, the safety profile in adolescents appears consistent with the overall population, and there were no meaningful dose-dependent differences observed. However, the adolescent safety database is limited by the small sample size and the timing of the primary database lock, which occurred while 20 subjects remained on treatment.

Evaluation of Pharmacokinetics

Plasma samples for PK assessment were collected in all adolescents enrolled in Study 301. Overall, brensocatib plasma exposure in adolescents is generally within the same range of the exposure in adults, although variability in adolescents was observed, likely attributable to the small sample size (n = 15 in the 10-mg group, and n = 16 in the 25-mg group). In addition, the PK data are available in about half the adults enrolled in each treatment arm. Refer to Section 14 for more detailed information. Despite this, the comparable exposure observed between adolescents and adults in Study 301 supports partial extrapolation of efficacy and safety.

Conclusion

The pathogenesis of NCFB, once established, progresses consistently across populations of different ages, with the unifying feature of cyclical airway inflammation and damage. As a DPP1 inhibitor, brensocatib targets the underlying neutrophil-driven inflammatory signature shared by all NCFB subpopulations. Collectively, the submitted data demonstrate similar efficacy and PK responses between adolescents and adults for both doses of brensocatib. These data, in combination with the knowledge of shared mechanisms and clinical progression of disease across age groups, support the approval of both doses of brensocatib in patients 12 to <18 years of age, relying partially on the extrapolation of the efficacy and safety data in adults. For a discussion of safety in adolescents to support this benefit-risk assessment, see Section 7.6.1.10.

6.3.3. Quality of Life-Bronchiectasis Respiratory Symptoms Doman Score

Issue

The Applicant initially proposed marketing of the 25-mg dose over the 10-mg dose (see Section 6.3.1) based in part on the nominal improvement in the QOL-B RSS among the 25-mg treatment group (b) (4) Although the Agency agrees that the QOL-B RSS is fit-for-purpose for the context of the brensocatib development program, (b) (4) (b) (4) Furthermore, there is uncertainty on the degree of improvement in the QOL-B RSS in Study 301 that is considered meaningful to patients. The review team considered the evidence provided in the application regarding whether the observed treatment effect demonstrated a clinically meaningful improvement in respiratory symptoms for subjects receiving brensocatib as compared to placebo.

Background

The Quality of Life–Bronchiectasis (QOL-B) is a patient-reported outcome (PRO) measure developed specifically for adult patients (≥18 years old) with NCFB, which assesses symptoms, functioning, and health-related quality of life based on a 1-week recall. The QOL-B contains 37 items across 8 domains, i.e., Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, and Treatment Burden. No total score is calculated; domain scores are standardized on a 0-to-100-point scale, with higher scores indicating better health-related quality of life. The Respiratory Symptoms Domain score (RSS) of the QOL-B was included as a key secondary endpoint in both Study 201 and Study 301. Adult subjects completed the QOL-B in their respective languages via an eDiary every 2 weeks from Baseline (Day 1) to Week 56.

The Agency recommends the use of anchor-based methods to establish meaningful change thresholds in clinical outcome assessment-based endpoints, although other methods (e.g., qualitative evidence) can be used per the FDA draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023). The Applicant administered two anchor measures for this purpose, the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC). However, the utility of PGIS and PGIC as anchors for evaluating within-patient

meaningful change in the QOL-B-based secondary endpoint is limited by the following: the broad concept of "overall status", which is not specific to bronchiectasis symptoms and/or impacts, assessed by both anchors; the long recall period of PGIC possibly resulting in recall bias; and a lack of qualitative data to support what amount of change on the anchors represents a meaningful improvement to patients (see Section 16.1.4.2). Additionally, the PGIS and PGIC were added to the study materials in Study 301 after study enrollment resulting in fewer than 20% of patients in the ITT population with non-missing QOL-B RSS at baseline having PGIS or PGIC data that could be used to assess patient perception of meaningful change (see Section 16.1.4.2).

To assess the comparability of the subsample with and without available PGIS and PGIC anchor data, the Agency requested the Applicant compare the subsamples on the following: distribution of QOL-B RSS, baseline characteristics, and demographic characteristics. Additionally, while the review team did not identify an ideal anchor variable in the Study 301 data that could be used to aid in the interpretation of meaningful change, the Agency requested the Applicant conduct supplemental anchor-based analyses using the usual activities (UA) item of the EuroQoL-5 Dimension-5 Levels questionnaire (EQ-5D-5L) as this item was administered to the full sample in Study 301. Notably, the interpretability of this anchor variable for the assessment of meaningful change on the QOL-B RSS is limited by the difference in the recall period of the UA item (i.e., "today") and the assessment period (i.e., "1 week") and of the QOL-B as well as by the difference in the concepts assessed by each (see Section 16.1.4.2).

The Applicant conducted anchor-based analyses using the PGIS and PGIC. Based on the mean and median change in QOL-B RSS from Baseline to Week 52 for subjects who experienced a 1-point improvement in PGIS as well as for patients who reported "minimally improved" and "much improved" on the PGIC, the Applicant proposed a meaningful change threshold range of an 11-point to 14-point improvement on the QOL-B RSS. While the Applicant's anchor-based analyses were largely appropriate, they did not take into account the number of patients who did not report an improvement in their overall status who would be misclassified as having a meaningful improvement at these threshold values. Additionally, the Applicant did not address the generalizability of results from the subsample with PGIS and PGIC anchor data to the full trial sample (see Section 16.1.4.3).

Assessment

The review team assessed the comparability of the subsamples with and without PGIS and PGIC anchor data on their QOL-B RSS, baseline characteristics, and demographics, and determined the results of the anchor-based meaningful change analyses could be generalized to the full trial sample (see Section 16.1.4.3). Additionally, the Agency conducted anchor-based analyses using the subsample with PGIS and PGIC data as well as a supplemental anchor-based analyses using the EQ-5D-5L UA item, which was administered to the full sample. As the two analyses resulted in similar meaningful change threshold ranges, the results of analyses using the UA item are not discussed in this review.

While the Applicant did not provide evidence from patient input to demonstrate that a 1-category improvement on PGIS or "minimally improved" and "much improved" represented a meaningful improvement to patients, the review team's assessment indicated these target anchor-categories would be reasonable for the analysis (see Section 16.1.4.6). Based on an assessment of the full distribution of QOL-B RSS, taking into account both the number of subjects who did not report

an improvement but would be misclassified as having a meaningful benefit and subjects' baseline symptom severity, the Agency identified a plausible range of clinically meaningful change thresholds between 14.8 and 20-point improvement on QOL-B RSS. Within in this meaningful change range, the differences in response rates between the Brensocatib 10 mg QD arm and the placebo arm are between 2.6% and 5.1%, and between the Brensocatib 25 mg QD arm and the placebo arm are between 3.1% and 5.2%. Based on these analyses, there is no evidence that either the brensocatib 10 mg or the brensocatib 25 mg represents a clinically meaningful improvement over placebo in QOL-B RSS (see Section 16.1.4.7).

Conclusion

Based on the evidence available to date, the QOL-B RSS is deemed fit-for-purpose in the context of the brensocatib development program; however, using both the Agency-determined and the Applicant-determined clinically meaningful change threshold range, there does not appear to be a clinically meaningful improvement in QOL-B RSS with either brensocatib dose in Study 301. The lack of a clinically meaningful change in QOL-B RSS does not affect the approvability of brensocatib on efficacy grounds as both trials met their primary endpoints, which are clinically meaningful. Furthermore, Study 301 met the first two key secondary endpoints, which are higher in the testing hierarchy than the QOL-B RSS and are clinically meaningful. The lack of clinically meaningful change in the QOL-B RSS (b) (4)

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The totality of nonclinical studies conducted support the approval and marketing of brensocatib. Nonclinical safety was evaluated in the following studies during development: safety pharmacology in the rat and dog; repeat-dose toxicology studies conducted in the rat and dog for durations up to 26 weeks and 39 weeks, respectively; a full battery of reproductive toxicology studies in rat and rabbit; genetic toxicology studies (in vitro bacterial reverse mutation (Ames) assay, in vitro mouse lymphoma cell thymidine kinase locus assay, and in vivo rat micronucleus assays), and 2-year rat and 6-month Tg.rasH2 mouse carcinogenicity studies. Nonclinical findings of note are summarized below (refer to Section 13 for additional details).

General Toxicology

In humans, loss of DPP1 function results in PLS, one of the hallmarks of which is severe oral inflammation (see Section 7.2 for further information). There were no adverse effects observed in the periodontium of rats administered up to 50 mg/kg/day brensocatib for 26 weeks (152 times the maximum recommended human dose [MRHD] on an AUC basis). Periodontal inflammation was not observed in the 28-day repeat dose toxicology study in dogs at exposures up to 50 times the MRHD. In the 6-month repeat dose toxicology study in dogs, severe periodontal disease was observed at the highest dose administered of 50 mg/kg (greater than 7 times the MRHD). The inflammation led to bleeding gums, tooth loss, as well as alveolar bone resorption/fibrosis of the jaw that resulted in decreased clinical condition and euthanasia of the affected animals at Week

18/19. In a 39-week repeat dose toxicology study in dogs, doses were lowered to mitigate the adverse effects on the periodontium. At exposures up to 5.4 times the MRHD, there were no adverse findings in the periodontium of dogs after 39 weeks of brensocatib administration.

Brensocatib is a cationic amphiphilic drug. Cationic amphiphilic drugs are known to cause phospholipidosis (PLD) in nonclinical species. Phospholipidosis, indicated by vacuolation and foamy macrophage accumulation, was observed in repeat-dose toxicology studies in both rats and dogs. PLD was evident in the lungs and mesenteric lymph nodes of rats administered 100 mg/kg/day for 28 days (202 times the MRHD on an AUC basis). After oral administration of 50 mg/kg/day brensocatib for 6 months, PLD was present in the lungs of rats indicating progression of the finding (152 times MRHD). After 28-day and 3-month treatment-free periods, respectively, PLD was not present in rats indicating recovery from this finding.

Phospholipidosis was not observed in 28-day repeat dose toxicology studies in dogs up to 50 times the MRHD. In dogs administered 50 mg/kg/day for 18 weeks, increased lysosomal accumulation was observed in alveolar macrophages by transmission electron microscopy (TEM), which is consistent with PLD (greater than 7 times the MRHD). PLD was also observed in lymphoid tissues and spleen with minimal to marked accumulations of vacuolated macrophages in all dogs given 50 mg/kg dose for 18 weeks. Complete recovery of the PLD findings at 50 mg/kg/day was observed after a 26-week treatment-free period. Macrophage accumulation of reduced severity was also observed in lungs of dogs administered 8 mg/kg/day for 26 weeks indicating progression of this finding (6 times the MRHD). In dogs administered 8 mg/kg/day brensocatib for 39 weeks, minimal PLD was observed in the lungs (5 times the MRHD). The relevance of phospholipidosis observed in animals to humans is not clear.

The kidney was also noted as a common site of toxicity between rats and dogs. Tubular vacuolation and basophilia were observed in rats administered 100 mg/kg for 28 days (202 times the MRHD). The tubular basophilia was recovered after a 28-day treatment-free period but tubular vacuolation was still present. Tubular basophilia in the kidneys was also evident in rats administered 50 mg/kg for 6 months (152 times MRHD). This finding correlated with an increase in N-acetyl-β-d-glucosaminidase (NAG) and the NAG/creatinine ratio in urine. The findings were recovered after a 3-month treatment-free period.

Tubular degeneration and vacuolation were also observed in dogs administered 75 mg/kg/day for 28 days (50 times the MRHD). Minimal to mild bilateral tubular basophilic regeneration at the corticomedullary junction was also observed in dogs administered 50 mg/kg/day for 18 weeks. This correlated to increases in NAG and NAG/creatinine ratio observed in urinalysis. There were no findings in the kidneys of dogs administered 8 mg/kg/day brensocatib for 39 weeks (7 times the MRHD). Sufficient exposure margins between the adverse kidney findings in nonclinical species and humans supported the continued clinical development of brensocatib with appropriate clinical monitoring.

Reproductive and Developmental Toxicology

In fertility studies, male and female rats did not show any impairments. However, in 26-week repeat dose toxicity studies in dogs, tubular degeneration and atrophy were observed in testes alongside germ cell degeneration and depletion at 8 mg/kg/day (6 times the MRHD). At higher doses (50 mg/kg/day), severe germ cell depletion was observed in the testis resulting in tubular atrophy and reduced testicular size within 18 weeks. Concurrently, Leydig cell hypertrophy and

hyperplasia was observed. The epididymis contained drastically reduced or no sperm. Following a 6-month recovery period, hypospermatogenesis was observed indicating incomplete recovery. In short-term repeat dose toxicity studies, similar changes were observed at much higher doses of 75 mg/kg/day (50 times MRHD). The nature of severity in testicular changes in short term versus long term studies indicate progression of toxicity at high multiples of human exposure.

In pregnant rats, the adverse skeletal malformation of bent scapula was observed at high doses (128 times MRHD). In pregnant rabbits, there was a decrease in body weight gain at 15 mg/kg and 50 mg/kg/day brensocatib (5 and 20 times the MRHD, respectively) with no accompanying fetal abnormalities. In the pre- and postnatal development study, no drug-related changes were observed in F1 pups or in F2 embryonic survival at oral maternal doses up to 20 mg/kg/day (17 times MRHD).

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

There are no small molecule inhibitors of DPP1 (cathepsin C) currently approved. Humans who carry biallelic loss-of-function variants in the gene for DPP1, *CTSC* (UniProt 2025), develop a constellation of clinical manifestations collectively known as PLS. Papillon-Lefèvre syndrome is a rare, inherited, autosomal recessive disease characterized by the development of chronic severe oral inflammation leading to gingivitis and periodontitis, hyperkeratosis, and, less commonly, organ-specific infections, such as pyogenic skin infections with rare serious liver abscesses and pneumonia reported (Almuneef et al. 2003; Ullbro et al. 2003; Sreeramulu et al. 2015; NORD 2019; OMIM 2025). Other rarer clinical features of PLS in order of reported relative frequency include stomatitis, hypotrichosis, nail changes, hyperhidrosis, intracranial calcifications, and neoplasms affecting the skin and ocular surface (Gorlin et al. 1964; Murthy et al. 2005; Alsaif et al. 2019; NORD 2019; OMIM 2025).

Although the clinical presentation of PLS is of an inflammatory condition with susceptibility to infection, the underlying mechanisms of immune dysregulation in DPP1 deficiency are not well-defined. Furthermore, there is mixed clinical and scientific evidence to support the notion that PLS is also an immunodeficiency predisposing to infectious complications (Pham et al. 2004; Dalgic et al. 2011; Sorensen et al. 2014; Sreeramulu et al. 2015). Since the most common syndrome-defining features of PLS are gingival/periodontal disease, hyperkeratosis, and infections, including severe infections, these were pre-defined by the Applicant as adverse events of special interest.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

Brensocatib is not currently approved in the United States or in any other foreign market; therefore, no postmarketing experience is available.

7.4. FDA Approach to the Safety Review

The evaluation of safety for brensocatib in subjects with NCFB is primarily based on the clinical data from Studies 301 and 201. Although both Studies 301 and 201 were similarly designed and enrolled similar populations, they differ in the length of the treatment periods (52-weeks and 24-weeks, respectively) and in some key aspects of the enrolled populations (e.g., inclusion of adolescents in 301 and exclusion of certain etiologies of bronchiectasis from 201); therefore, safety analyses were conducted and are presented separately. We explored pooled analyses for better characterization of some signals, where noted. For each trial, all safety analyses were conducted on the safety population or safety analysis set, defined as all subjects who received at least one dose of study drug. All AEs presented are considered treatment-emergent adverse events (TEAEs), defined as AEs that started or worsened in severity on or after the first dose and within 28 days after the last dose of study drug.

7.5. Adequacy of the Clinical Safety Database

The duration of exposure for Studies 301 and 201 is presented separately in Table 23 and Table 24, respectively.

Table 23. Duration of Exposure, Safety Population, Study 301

Parameter	Brensocatib 10 mg N=582	Brensocatib 25 mg N=574	Placebo N=563
Duration of treatment, weeks			
Mean (SD)	48.5 (10.6)	48.7 (10.7)	48.5 (10.7)
Median (Q1, Q3)	52 (51.2, 52.3)	52 (51.3, 52.3)	52 (51.3, 52.3)
Min, max	0.1, 59.7	0.9, 57.4	0.9, 57.9
Total exposure (person years)	541	536	523
Subjects treated, by duration, n(%)			
<12 weeks	17 (2.9)	17 (3.0)	18 (3.2)
≥12 to <24 weeks	17 (2.9)	19 (3.3)	16 (2.8)
≥24 to <36 weeks	24 (4.1)	15 (2.6)	19 (3.4)
≥36 to <52 weeks	181 (31.1)	188 (32.8)	176 (31.3)
≥52 to <56 weeks	340 (58.4)	328 (57.1)	331 (58.8)
≥56 to <60 weeks	3 (0.5)	7 (1.2)	3 (0.5)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 52 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 24. Duration of Exposure, Safety Population, Study 201

Parameter	Brensocatib 10 mg N=81	Brensocatib 25 mg N=89	Placebo N=85
Duration of treatment, weeks			
Mean (SD)	22.4 (4.9)	21.8 (6)	21.7 (5.8)
Median (Q1, Q3)	24 (23.7, 24.1)	24.1 (23.7, 24.3)	24 (23.7, 24.1)
Min, max	1.9, 26	0.7, 25.4	0.3, 25.1
Total exposure (person years)	35	37	35

Parameter	Brensocatib 10 mg N=81	Brensocatib 25 mg N=89	Placebo N=85
Subjects treated, by duration, n(%)			
<12 weeks	8 (9.9)	10 (11.2)	8 (9.4)
≥12 to <16 weeks	0	1 (1.1)	2 (2.4)
≥16 to <20 weeks	1 (1.2)	3 (3.4)	5 (5.9)
≥20 to <24 weeks	20 (24.7)	18 (20.2)	20 (23.5)
≥24 to <28 weeks	52 (64.2)	57 (64.0)	50 (58.8)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 24 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Collectively, the safety database included a total of 1,974 subjects of whom 663 received brensocatib 10 mg, 663 received brensocatib 25 mg, and 648 received placebo. The duration of treatment was balanced between all arms within both studies. Overall, the safety database provided by the Applicant appears adequate to evaluate the safety of brensocatib for an NCFB population.

7.6. Safety Results

7.6.1. Safety Results, Study 301

7.6.1.1. Overview of Adverse Events Summary, Study 301

The overview of the adverse events occurring in Study 301 is provided in Table 25. The proportion of subjects experiencing any AEs was generally balanced between the treatment and placebo groups. The majority of the AEs were mild to moderate in severity, and the placebo group had a higher proportion of subjects experiencing severe AEs and serious adverse events (SAEs).

Table 25. Overview of Adverse Events, Safety Population, Study 301

Event Category	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
SAE	101 (17.4)	97 (16.9)	108 (19.2)
SAEs with fatal outcome	3 (0.5)	4 (0.7)	7 (1.2)
Life-threatening SAEs	7 (1.2)	0	3 (0.5)
SAEs requiring hospitalization	95 (16.3)	90 (15.7)	103 (18.3)
SAEs resulting in substantial disruption of normal life functions	8 (1.4)	3 (0.5)	5 (0.9)
Other	9 (1.5)	10 (1.7)	13 (2.3)
AE leading to permanent discontinuation of study drug	25 (4.3)	22 (3.8)	23 (4.1)
AE leading to dose modification of study drug	46 (7.9)	63 (11.0)	58 (10.3)
AE leading to interruption of study drug	46 (7.9)	63 (11.0)	58 (10.3)

Event Category	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any AE	452 (77.7)	440 (76.7)	448 (79.6)
Severe and worse	75 (12.9)	67 (11.7)	90 (16.0)
Moderate	207 (35.6)	205 (35.7)	186 (33.0)
Mild	170 (29.2)	168 (29.3)	172 (30.6)

Source: adae.xp; Software: R
Duration is 52 weeks.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Study 301

The deaths reported in Study 301 are summarized in Table 26. Overall, the deaths were infrequent and balanced between the treatment groups. A total of 14 subjects died in Study 301, seven of whom received brensocatib, three in the 10-mg dose group and four in the 25-mg dose group. The death secondary to *Aspergillus* infection is discussed in the context of severe infection AESIs in Section 7.6.1.6 There were no AEs leading to death reported for any adolescent subjects.

Table 26. Deaths, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any AE leading to death	3 (0.5)	4 (0.7)	7 (1.2)
Aspergillus infection	1 (0.2)	0	0
Acute respiratory failure	1 (0.2)	0	1 (0.2)
Bronchiectasis	1 (0.2)	0	1 (0.2)
Pneumonia	0	1 (0.2)	1 (0.2)
General physical health deterioration	0	1 (0.2)	0
Myocardial infarction	0	1 (0.2)	0
Road traffic accident	0	1 (0.2)	0
Cardiac arrest	0	0	1 (0.2)
Cardio-respiratory arrest	0	0	1 (0.2)
Cervical vertebral fracture	0	0	1 (0.2)
Hemoptysis	0	0	1 (0.2)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

The death narratives provided by the Applicant were reviewed. Among the seven deaths between the brensocatib treatment arms, four were attributable to bronchiectasis or NCFB sequelae (e.g., infection, pneumonia, respiratory failure), which are not unexpected in this population. Narrative review of the remaining three deaths attributable to other causes, all occurring in the brensocatib 25-mg group, are briefly summarized below.

- Subject (b) (6) A 56-year-old white male, ex-smoker with moderate NCFB (BSI score of 5 and *P. aeruginosa* negative at screening) and comorbidities of hypertension, type 2 diabetes mellitus, and obesity. He presented to the emergency department of a local hospital where he could not be revived after multiple resuscitation attempts. The Investigator

and Applicant assessed the event to be unrelated to study treatment given that the subject's medical history of smoking and type-2 diabetes put him at high risk for heart disease.

- Subject (b) (6) A 76-year-old white female with severe bronchiectasis (BSI score of 10 and *P. aeruginosa* positive at screening). The subject sustained vertebral fractures caused by her age, weight, and overall sedentary lifestyle because of her underlying poor mobility. Her oral intake gradually decreased over the course of 3 to 4 months leading to general deterioration of her health status and eventual death at home. The event was labeled by the Investigator and Applicant as secondary to her underlying disease and vertebral fractures and not related to study treatment.
- Subject (b) (6) A 63-year-old white female was struck by a motor vehicle causing severe internal organ damage resulting in death.

We agree with the Applicant's assessment that these deaths were unlikely related to study drug. No clear patterns in the causes of death emerge that suggest relatedness to study drug, as compared to relatedness to underlying disease. Overall, Study 301 had a low incidence of death given the severity of illness of the enrolled population.

7.6.1.3. Serious Adverse Events, Study 301

A total of 306 (17.8%) subjects experienced at least one SAE in Study 301. In general, the placebo group demonstrated a greater proportion of subjects with any SAE (19.2%) compared to either of the treatment groups (17.4% and 16.9% in brensocatib 10-mg and brensocatib 25-mg groups, respectively). Serious Adverse Events occurring in two or more subjects in the Safety Population are presented in Table 27. The most common SAEs reported were bronchiectasis, pneumonia, and COVID-19.

Table 27. Serious Adverse Events by Preferred Term Occurring in More Than Two Subjects, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any SAE	101 (17.4)	97 (16.9)	108 (19.2)
Bronchiectasis	47 (8.1)	48 (8.4)	67 (11.9)
Pneumonia	11 (1.9)	13 (2.3)	16 (2.8)
COVID-19	4 (0.7)	9 (1.6)	6 (1.1)
Hemoptysis	3 (0.5)	1 (0.2)	6 (1.1)
Atrial fibrillation	2 (0.3)	1 (0.2)	4 (0.7)
Pseudomonas infection	2 (0.3)	2 (0.3)	2 (0.4)
Acute respiratory failure	2 (0.3)	1 (0.2)	2 (0.4)
Pulmonary embolism	2 (0.3)	1 (0.2)	2 (0.4)
Cataract	1 (0.2)	0	3 (0.5)
Influenza	2 (0.3)	1 (0.2)	1 (0.2)
Urinary tract infection	1 (0.2)	2 (0.3)	1 (0.2)
Appendicitis	2 (0.3)	0	1 (0.2)
Herpes zoster	0	2 (0.3)	1 (0.2)
Lung abscess	0	2 (0.3)	1 (0.2)
Pancreatitis acute	0	1 (0.2)	2 (0.4

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Alcohol poisoning	1 (0.2)	0	1 (0.2)
Arthralgia	0	1 (0.2)	1 (0.2)
Cardiac failure acute	1 (0.2)	1 (0.2)	0
Coronavirus infection	1 (0.2)	0	1 (0.2)
COVID-19 pneumonia	1 (0.2)	0	1 (0.2)
Hypertension	0	1 (0.2)	1 (0.2)
Intestinal obstruction	1 (0.2)	1 (0.2)	0
Joint dislocation	2 (0.3)	0	0
Lower respiratory tract infection	1 (0.2)	1 (0.2)	0
Meniscus injury	2 (0.3)	0	0
Myocardial infarction	1 (0.2)	1 (0.2)	0
Ovarian cyst	1 (0.2)	1 (0.2)	0
Pneumonia aspiration	0	0	2 (0.4)
Pneumonia bacterial	0	1 (0.2)	1 (0.2)
Road traffic accident	1 (0.2)	1 (0.2)	0
Sepsis	1 (0.2)	0	1 (0.2)
Sinusitis	2 (0.3)	0	0

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event.

All SAEs occurring in more than two subjects had a 95% CI for the risk difference that included the null between placebo and either treatment group with the exception of bronchiectasis. Both brensocatib groups demonstrated a reduction in relative risk compared to placebo in the incidence of bronchiectasis SAEs, which is consistent with the overall treatment effect of brensocatib. There were four hepatobiliary SAEs, all of which occurred in the brensocatib 25-mg group, with no clear trend by preferred term (PT)(e.g., cholangitis, cholelithiasis, hepatic steatosis, and hepatic function abnormal). Hepatobiliary AEs are discussed further in Section 7.6.1.8. There were five reproductive SAEs, four of which occurred in the 10-mg group and one in the 25-mg group, among which there were no clear trends by PT. Importantly, none of these reproductive SAEs involved testicular function or other male gonadal dysfunction observed in the animal fertility toxicology studies (Section 7.1). Overall, the analysis of the SAEs consisted primarily of expected events in the context of underlying NCFB and did not reveal clear patterns to suggest treatment relatedness.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Study 301

Adverse events leading to treatment discontinuation are summarized in Table 28 below. Overall, AEs leading to treatment discontinuation were infrequent and appeared relatively balanced across the treatment groups with frequencies of 4.3% in the brensocatib 10 mg, 3.8% in the brensocatib 25-mg group, and 4.1% in the placebo group. However, there were differences in the distribution of AEs by PT across groups with COVID-19, fatigue, dizziness, headache, pruritus, and rash occurring among the brensocatib groups only.

Table 28. Adverse Events Leading to Treatment Discontinuation by Preferred Term Occurring in More Than Two Subjects, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any AE leading to discontinuation	25 (4.3)	22 (3.8)	23 (4.1)
Diarrhea	2 (0.3)	0	0
Nausea	0	2 (0.3)	1 (0.2)
Fatigue	0	2 (0.3)	0
COVID-19	0	2 (0.3)	0
Dizziness	2 (0.3)	1 (0.2)	0
Headache	2 (0.3)	3 (0.5)	0
Cough	0	2 (0.3)	0
Bronchiectasis	2 (0.3)	2 (0.3)	4 (0.7)
Pruritus	2 (0.3)	0	0
Rash	2 (0.3)	1 (0.2)	0

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AE, adverse event N, number of subjects in treatment arm; n, number of subjects with adverse event

There were no risk differences in AEs leading to discontinuation of the study medication where the 95% CIs excluded the null. No patterns across system organ class or PT emerged, except general disorders and administration site conditions. There were 4 subjects in the brensocatib 25-mg dose group who experienced fatigue (2), generalize edema (1) and malaise (1), and none in the brensocatib 10-mg or placebo groups. The most common AEs leading to study drug discontinuation include bronchiectasis, headache, and rash. Headache and rash are further discussed in Section 7.6.1.5. Overall, AEs leading to treatment discontinuation in the phase 3 program were balanced between the treatment and placebo groups.

7.6.1.5. Treatment-Emergent Adverse Events and Adverse Reactions, Study 301

A total of 1340 (78.0%) subjects experienced at least one TEAE during the 52-week treatment period, and the incidence of TEAEs were generally balanced between treatment groups. The most common AEs, limited to those occurring in ≥2% of subjects are presented in Table 29.

Table 29. Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥2% Subjects, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any AE	452 (77.7)	440 (76.7)	448 (79.6)
COVID-19	92 (15.8)	120 (20.9)	89 (15.8)
Bronchiectasis	49 (8.4)	49 (8.5)	67 (11.9)
Headache	39 (6.7)	49 (8.5)	39 (6.9)
Nasopharyngitis	45 (7.7)	36 (6.3)	43 (7.6)
Cough	41 (7.0)	35 (6.1)	36 (6.4)
Urinary tract infection	28 (4.8)	32 (5.6)	33 (5.9)
Sinusitis	28 (4.8)	25 (4.4)	28 (5.0)

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Pyrexia	24 (4.1)	26 (4.5)	25 (4.4)
Pneumonia	25 (4.3)	22 (3.8)	28 (5.0)
Diarrhea	26 (4.5)	21 (3.7)	27 (4.8)
Back pain	13 (2.2)	17 (3.0)	35 (6.2)
Arthralgia	26 (4.5)	18 (3.1)	20 (3.6)
Fatigue	19 (3.3)	22 (3.8)	21 (3.7)
Hemoptysis	19 (3.3)	17 (3.0)	26 (4.6)
Upper respiratory tract infection	23 (4.0)	21 (3.7)	16 (2.8)
Hypertension	28 (4.8)	13 (2.3)	17 (3.0)
Influenza	26 (4.5)	10 (1.7)	22 (3.9)
Rash	16 (2.7)	26 (4.5)	13 (2.3)
Dyspnea	16 (2.7)	15 (2.6)	22 (3.9)
Nausea	12 (2.1)	12 (2.1)	21 (3.7)
Pain in extremity	13 (2.2)	8 (1.4)	17 (3.0)
Dizziness	12 (2.1)	13 (2.3)	9 (1.6)
Constipation	13 (2.2)	9 (1.6)	12 (2.1)
Oropharyngeal pain	12 (2.1)	12 (2.1)	9 (1.6)
Non-cardiac chest pain	11 (1.9)	10 (1.7)	12 (2.1)
Dry skin	9 (1.5)	16 (2.8)	7 (1.2)
Pruritus	10 (1.7)	8 (1.4)	12 (2.1)
Gingival pain	8 (1.4)	6 (1.0)	13 (2.3)
Bronchitis	5 (0.9)	8 (1.4)	14 (2.5)
Rhinorrhea	5 (0.9)	7 (1.2)	13 (2.3)
Hyperkeratosis	5 (0.9)	15 (2.6)	3 (0.5)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

A threshold frequency of ≥1% in either brensocatib group compared to placebo was used to identify adverse reactions from Table 29. These adverse reactions are presented in Table 30. The adverse reactions of rash, dry skin, and hyperkeratosis are skin-related disorders for which additional analyses were performed based on preferred grouping of terms recommended by the Division of Dermatology and Dental Products (DDD). As a result, the total number of events displayed in Table 30 are based on those analyses. Refer to Sections 7.6.1.6 and 7.7.2 for further information.

Table 30. Adverse Reactions by Preferred Term Occurring in ≥2% Subjects and With a Frequency ≥1% in Brensocatib Arms Compared to Placebo, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Any AE	452 (77.7)	440 (76.7)	448 (79.6)
Upper respiratory tract infection[1]	92 (15.8)	120 (20.9)	89 (15.8)
Headache	39 (6.7)	49 (8.5)	39 (6.9)
Rash[2]	25 (4.3)	35 (6.1)	22 (3.9)
Dry skin[2]	17 (2.9)	25 (4.4)	8 (1.4)

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Hyperkeratosis[2]	8 (1.4)	16 (2.8)	5 (0.9)
Hypertension	28 (4.8)	13 (2.3)	17 (3.0)

Source: adae.xpt; Software: R
[1] Denotes the grouping of the following adverse reactions: coronavirus infection, COVID-19, influenza, upper respiratory tract infection, viral infection, and viral upper respiratory tract infection.
[2] Denotes adverse reactions based upon recommended grouping of terms per Division of Dermatology and Dental products consultant.
Duration is 52 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Adverse events of upper respiratory tract infections, rash, and hyperkeratosis were more common in the brensocatib 25-mg dose compared to placebo, where 95% CIs of the risk difference excluded the null. Most of the upper respiratory tract infections cases were mild-to-moderate in severity. Serious upper respiratory tract infections were primarily due to COVID-19 of which there were 4, 9, and 6 SAE cases in the brensocatib 10-mg dose group, brensocatib 25-mg dose group, and placebo groups, respectively (Table 27). Most of the rash and hyperkeratosis cases were mild with one case leading to treatment discontinuation in the brensocatib 25-mg dose group. Hyperkeratosis and other skin-related disorders are discussed in greater depth in Sections 7.6.1.6 and 7.7.2. Review of the common AEs did not reveal any other significant safety concerns.

7.6.1.6. Adverse Events of Special Interest, Study 301

Adverse events of special interest were predefined based on the nonclinical data (Sections 7.1 and 13) and the most common, syndrome-defining clinical characteristics of PLS, an inherited disease of DPP1 deficiency (refer to Section 7.2 for further details). The most common clinical features of PLS include hyperkeratosis, gingival/periodontal events, and serious infections, including pneumonia. The groupings of terms for each AESI category were reviewed and found appropriate for gingivitis/periodontitis, pneumonia, and other severe infections. Consultants from DDD did not agree with the excessively broad PT grouping of skin disorders under hyperkeratosis and provided guidance on grouping of terms for the assessment of all skin-related AEs (Section 17). Review of hyperkeratosis events by expert recommended groupings are described in Section 7.7.2.

Hyperkeratosis

Skin examination procedures were conducted throughout the study on all subjects, and the details of skin assessments are further described in Section 15.1.3.2. A summary of all hyperkeratosis events as defined by the Applicant are displayed in Table 31 below. While the overall frequency of hyperkeratosis was generally low, hyperkeratosis events occurred with greater frequency in the brensocatib treatment groups. The largest number of events occurred in the brensocatib 25-mg group with a risk difference of 2.3 and 95% confidence intervals that exclude the null. In general, most hyperkeratosis events were mild, and most of the few moderate events occurred in the 25-mg treatment arm. A single subject in the 25-mg treatment arm discontinued treatment, and three subjects in the 25-mg arm had treatment interruptions because of hyperkeratosis.

Among the 25 affected subjects, only one was an adolescent, who received brensocatib 10 mg and had a mild event that did not require dermatology referral and self-resolved.

Table 31. Applicant-Defined Hyperkeratosis AESIs by Preferred Term, Safety Population, Study 301

Adverse Event Category	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Subjects with at least 1 hyperkeratosis event	8 (1.4)	17 (3.0)	4 (0.7)
Eczema	0	1 (0.2)	0
Eczema asteatotic	0	1 (0.2)	0
Exfoliative rash	0	0	1 (0.2)
Hyperkeratosis	5 (0.9)	15 (2.6)	3 (0.5)
Keratosis pilaris	0	1 (0.2)	0
Palmoplantar keratoderma	2 (0.3)	0	0
Seborrheic keratosis	1 (0.2)	0	0
Maximum severity			
Moderate	1 (0.2)	4 (0.7)	0
Mild	7 (1.2)	13 (2.3)	4 (0.7)
Resulting in discontinuation	0	1 (0.2)	0

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AESI, adverse event of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event

Review of the subject narratives for hyperkeratosis AESIs revealed a total of 21 out of 25 subjects (n=7, brensocatib 10 mg; n=13, brensocatib 25 mg; n=1, placebo) were referred to a dermatologist for further evaluation at the investigator's discretion. Among these 21 subjects, all were confirmed to have hyperkeratosis, and topical emollients and/or corticosteroids were prescribed for 5, 7, and 1 subjects in the brensocatib 10 mg, brensocatib 25 mg, and placebo arms, respectively.

The dose-dependent nature of hyperkeratosis AESIs and its implications for dose selection and labeling considerations are further discussed in Sections 7.7.1 and 7.7.2.

Gingival/Periodontal Events

Adult subjects conducted self-monitoring, and adolescents underwent investigator-administered oral examinations throughout the study. Details on oral assessments are described in Section 15.1.3.2 and a summary of all gingival/periodontal events are displayed in Table 32 below.

Table 32. Applicant-Defined Gingival/Periodontal AESI by Preferred Term, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Subjects with at least 1 periodontal/gingival event	8 (1.4)	12 (2.1)	15 (2.7)
Gingival bleeding	2 (0.3)	0	1 (0.2)
Gingival discomfort	0	0	1 (0.2)
Gingival disorder	4 (0.7)	6 (1.0)	7 (1.2)

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Gingival pain	0	1 (0.2)	1 (0.2)
Gingival recession	0	1 (0.2)	0
Gingivitis	1 (0.2)	2 (0.3)	1 (0.2)
Noninfective gingivitis	0	0	1 (0.2)
Oral pain	0	1 (0.2)	0
Periodontal disease	0	0	1 (0.2)
Periodontitis	1 (0.2)	2 (0.3)	2 (0.4)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AESI, adverse event of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event

Gingival/periodontal events were generally infrequent with lower incidence in the brensocatib 10-mg arm (1.4%) compared to brensocatib 25 mg (2.1%) and placebo (2.7%) arms. Events were generally mild or moderate with one severe event occurring in the placebo arm. Treatment discontinuation because of these events occurred in 2, 1, and 1 subjects from the brensocatib 10 mg, brensocatib 25 mg, and placebo arms, respectively. The most common PT reported was gingival disorder followed by periodontitis. Among the 35 subjects with periodontal/gingival events, 3 subjects, 1 from each treatment group, met the protocol-definition of severe periodontal disease.

Review of the periodontal/gingival data from Study 301 demonstrates increased frequency of events in placebo compared to treatment groups, a finding that is incongruent with the higher frequency of dental AESIs among the brensocatib-treated subjects in Study 201 (Sections 7.6.2.6 and 7.7.1). In Study 301, excluded subjects with periodontal disease and throughout the study assessment of periodontal disease relied upon subjects self-monitoring signs and reporting their findings upon active solicitation at study visits. Study 301 subjects were only evaluated by a dentist when signs or symptoms developed and were reported to the investigator (Section 15.1.3.2). In contrast, Study 201 subjects underwent a thorough baseline oral examination by a dentist, periodic follow-up examinations by a dentist, and dental inspections by the investigator at each visit, in addition to subject self-monitoring and reporting (Section 15.2.3.2). Consequently, Study 201 subjects underwent more comprehensive oral examinations by both the investigator and a dentist. It is likely that the reliance on subject self-reporting to trigger evaluation by a dental expert was not sufficiently sensitive to capture all possible gingival/periodontal events in Study 301. Refer to Sections 7.6.2.6 and 7.7.1 for details and additional discussion.

Pneumonia

Table 33 displays a summary of all pneumonia AESIs from Study 301. The frequency of pneumonia AESIs was lower in the brensocatib arms compared to placebo, which may be reflective of the brensocatib treatment effect. Pneumonia events were mostly moderate or mild with few severe events. There were two fatal events of pneumonia, one in the brensocatib 25-mg arm and one in the placebo arm, attributed to the subjects' underlying NCFB by investigators. Overall, treatment discontinuations secondary to pneumonia were rare.

Table 33. Applicant-Defined Pneumonia AESIs by Preferred Term, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Subjects with at least 1-pneumonia event	23 (4.0)	27 (4.7)	33 (5.9)
Beta hemolytic streptococcal infection	0	0	1 (0.2)
Eosinophilic pneumonia	0	1 (0.2)	0
Pneumonia	23 (4.0)	22 (3.8)	28 (5.0)
Pneumonia aspiration	0	0	1 (0.2)
Pneumonia bacterial	0	2 (0.3)	2 (0.4)
Pneumonia influenza	0	0	1 (0.2)
Pneumonia necrotizing	0	1 (0.2)	0
Pneumonia pneumococcal	0	1 (0.2)	1 (0.2)
Pneumonia pseudomonal	0	1 (0.2)	0
Pulmonary tuberculosis	0	0	1 (0.2)
Maximum severity			
Death	0	1 (0.2)	1 (0.2)
Life-threatening	0	1 (0.2)	1 (0.2)
Severe	6 (1.0)	9 (1.6)	13 (2.3)
Moderate	14 (2.4)	12 (2.1)	16 (2.8)
Mild	3 (0.5)	4 (0.7)	2 (0.4)
Serious	11 (1.9)	16 (2.8)	19 (3.4)
Deaths	0	1 (0.2)	1 (0.2)
Resulting in discontinuation	1 (0.2)	2 (0.3)	2 (0.4)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; AESI, adverse event of special interest

Notably, there was a single case of eosinophilic pneumonia that occurred in subject (b) (6) (b) (6) a 66-year-old white female and ex-smoker with a history of asthma, allergic rhinitis, and vitamin B12 deficiency, who was randomized to brensocatib 25 mg. Three days after starting treatment she received a COVID-19 vaccination. Peripheral eosinophilia was identified on Day 31 and persisted until Day 45. Also on Day 31, she reported cough with sputum, and a chest x-ray showed a peripheral opacity thought to represent an eosinophilic pneumonia. A bronchoscopy with bronchoalveolar lavage showed an elevated level of eosinophils (18%). She was treated with oral prednisolone, and study treatment was permanently withdrawn. The Applicant reported the event as unrelated to study treatment given the subject's history of asthma and recent administration of COVID-19 vaccination.

We agree with the Applicant that there are alternate possible etiologies for the subject's eosinophilic pneumonia; however, the possibility of drug relatedness cannot be excluded. There were no other cases of eosinophilic pneumonia in the clinical development program. Two other cases of organ tissue infiltration with eosinophils occurred with one in the brensocatib 10-mg group (eosinophilic gastritis in a subject with chronic gastritis and pernicious anemia) and one in the placebo group (eosinophilic esophagitis). Furthermore, events of increased eosinophil counts were rare, occurring in a total of nine subjects with histories of asthma and/or increased peripheral blood eosinophils, which were equally distributed across all three treatment arms. Collectively, the data do not demonstrate a clear pattern of drug-related eosinophilic reaction.

Overall, this review of the pneumonia AESI data did not raise any safety concerns for the use of brensocatib in the proposed population.

Other Severe Infections

Severe infections were appropriately defined as any infection requiring treatment with parenteral antibiotics, antivirals, or antifungal agents, clinical endoparasitosis, and opportunistic infection. Table 34 summarizes the incidence of severe infections AESIs for Study 301.

Table 34. Applicant-Defined Severe Infection AESIs by Preferred Term, Safety Population, Study 301

Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Subjects with at least 1 severe infection event	4 (0.7)	7 (1.2)	4 (0.7)
Achromobacter infection	0	0	1 (0.2)
Aspergillus infection	1 (0.2)	0	0
Citrobacter test positive	0	0	1 (0.2)
Herpes zoster	0	2 (0.3)	0
Klebsiella infection	0	1 (0.2)	0
Lung abscess	0	1 (0.2)	0
Periorbital cellulitis	0	0	1 (0.2)
Post procedural complication	0	1 (0.2)	0
Pseudomonas infection	0	1 (0.2)	0
Pyelonephritis	1 (0.2)	0	0
Sinusitis	1 (0.2)	0	0
Tinea pedis	0	1 (0.2)	0
Tuberculosis	0	0	1 (0.2)
Urinary tract infection	1 (0.2)	1 (0.2)	0
Maximum severity			
Death	1 (0.2)	0	0
Life-threatening	0	0	0
Severe	1 (0.2)	2 (0.3)	0
Moderate	2 (0.3)	4 (0.7)	4 (0.7)
Mild	0	1 (0.2)	0
Serious	3 (0.5)	4 (0.7)	2 (0.4)
Deaths	1 (0.2)	0	0
Resulting in discontinuation	1 (0.2)	0	1 (0.2)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: AESI, adverse event of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event

Severe infections were rare events of mostly moderate intensity, and there were no trends observed among the reported PTs. There was one death in the 10 mg brensocatib arm of a 67-year-old female subject with a history of severe bronchiectasis (BSI score 14, ≥3 pulmonary exacerbations) and multiple comorbidities who succumbed to *Aspergillus fumigatus* infection complicated by polymicrobial infections with COVID-19, *P. aeruginosa*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* despite maximal therapy with antifungals, antivirals, and antibiotics. This case is unlikely related to brensocatib therapy and most likely related to her long-standing severe NCFB, which, in late stages, is characterized by infection with these pathogens (Section 3). Overall, review of the severe infection AESI data did not raise any safety concerns about undue risk of opportunistic infections or immunosuppression with brensocatib.

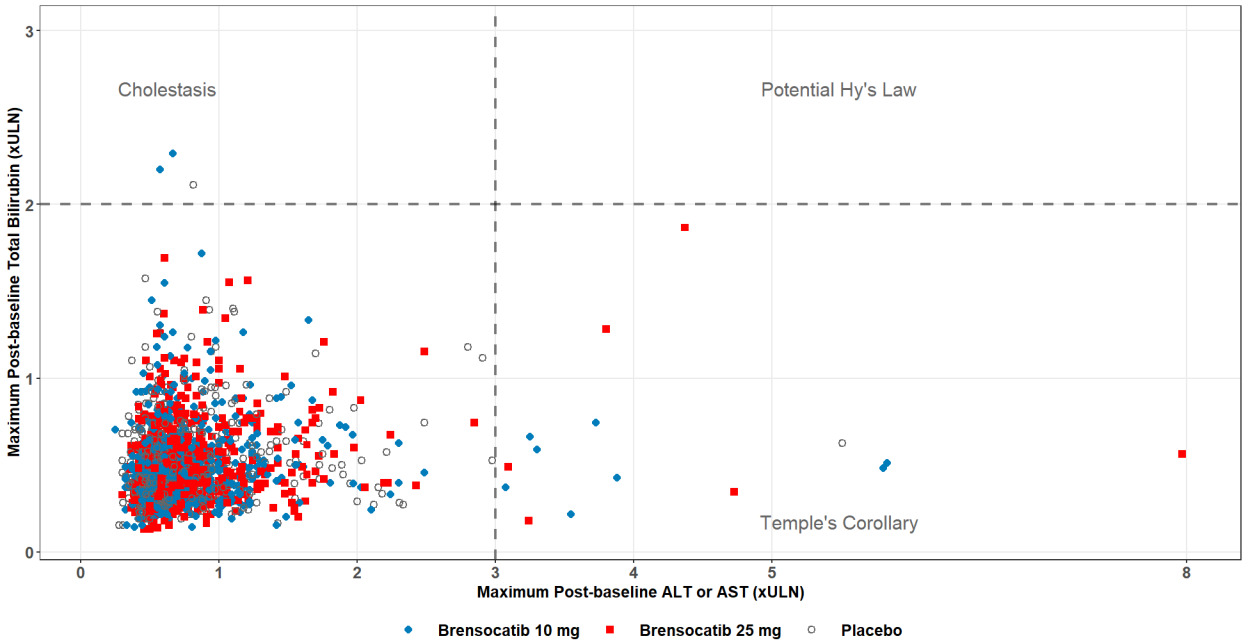
7.6.1.7. Laboratory Findings, Study 301

The Applicant conducted analyses of clinical laboratory results including chemistry and hematologic parameters. Analyses included the changes in mean values over time, changes in individual subjects over time, and potentially clinically significant values. There were no apparent clinically meaningful trends or mean changes from baseline observed in any hematologic or chemistry parameters. Potentially clinically significant values were infrequent and balanced between groups. There was a greater frequency of high bicarbonate values (exceeding 30 mEq/L) in subjects in the brensocatib 25-mg dose group compared to placebo, with the 95% CI of between group risk difference excluding the null. The frequencies were relatively low (6.2%, 6.6%, and 3.7% for brensocatib 10 mg, brensocatib 25 mg, and placebo, respectively). There was little to no change in bicarbonate from baseline over time in all three groups. In Study 201, this trend was observed in the opposite direction with a higher frequency in the placebo group. Patients with severe obstructive lung disease may also have elevated bicarbonate levels at baseline. Therefore, the clinical significance of this finding is unclear.

7.6.1.8. Assessment of Drug-Induced Liver Injury, Study 301

This review assessed the potential for DILI by correlating maximum bilirubin with maximum ALT or AST. This is displayed graphically in Figure 8.

Figure 8. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 301



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot …" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening…."
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

There were no potential Hy's Law cases demonstrated by the absence of cases in the upper right quadrant; however, there are several Temple's corollary cases falling within the bottom right quadrant.

Review of liver biochemistry analytes, summarized in Table 35 identified a higher frequency of ALT levels >3x the upper limit of normal (ULN) among subjects in both brensocatib groups with risk differences of 1.2 (10 mg) and 0.9 (25 mg) compared to placebo, with 95% CIs excluding the null. Similar increases of >3x ULN were observed for AST; however, the 95% CI did include the null. All other liver biochemistry analytes demonstrated comparable frequencies of increases above the ULN across treatment groups.

Table 35. Liver Biochemistry Analyte Values Above Upper Limit Normal, Safety Population, Study 301

Laboratory Parameter	Brensocatib 10 mg N=582 n/N_w (%)	Brensocatib 25 mg N=574 n/N_w (%)	Placebo N=563 n/N_w (%)
Alkaline phosphatase, high (U/L)			
>1.5X ULN	24/581 (4.1)	23/573 (4.0)	14/561 (2.5)
>2X ULN	5/581 (0.9)	4/573 (0.7)	5/561 (0.9)
>3X ULN	0/581 (0)	1/573 (0.2)	3/561 (0.5)

Laboratory Parameter	Brensocatib 10 mg N=582 n/N_w (%)	Brensocatib 25 mg N=574 n/N_w (%)	Placebo N=563 n/N_w (%)
Alanine aminotransferase, high (U/L)			
>3X ULN*	7/581 (1.2)	5/573 (0.9)	0/561 (0)
>5X ULN	0/581 (0)	1/573 (0.2)	0/561 (0)
>10X ULN	0/581 (0)	0/573 (0)	0/561 (0)
Aspartate aminotransferase, high (U/L)			
>3X ULN	2/581 (0.3)	3/573 (0.5)	1/561 (0.2)
>5X ULN	2/581 (0.3)	0/573 (0)	1/561 (0.2)
>10X ULN	0/581 (0)	0/573 (0)	0/561 (0)
Bilirubin, total, high (mg/dL)			
>1.5X ULN	4/581 (0.7)	4/573 (0.7)	2/561 (0.4)
>2X ULN	2/581 (0.3)	0/573 (0)	1/561 (0.2)
>3X ULN	0/581 (0)	0/573 (0)	0/561 (0)

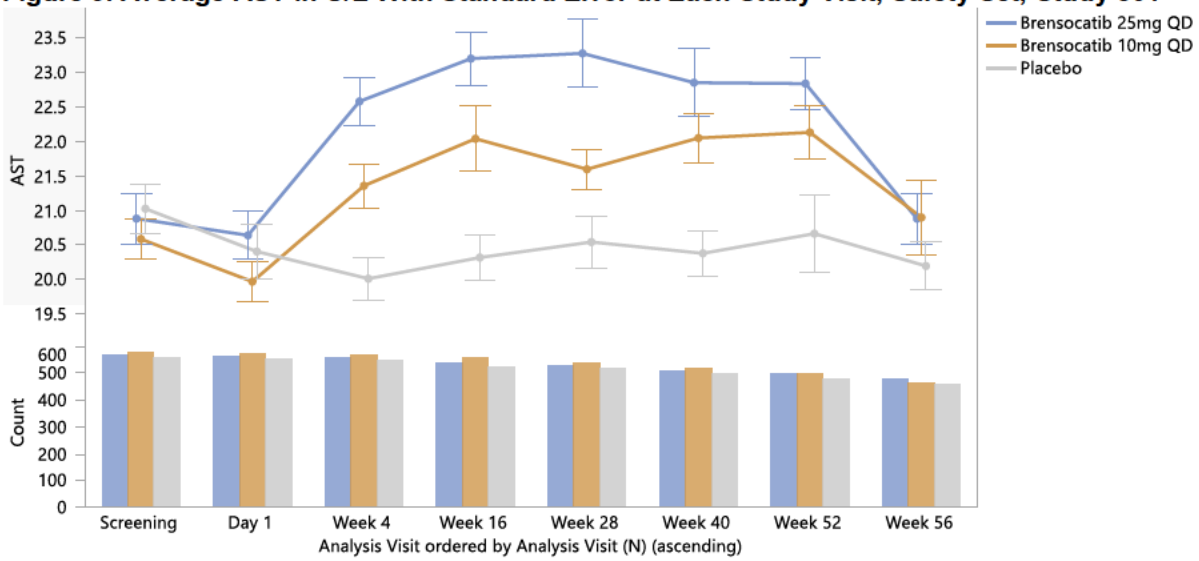
Source: adlb.xpt; Software: R
Duration is 52 weeks.
* Risk difference with 95% confidence interval (CI) between total treatment and comparator where the CI excludes the null occurs for ALT >3x ULN in both treatment groups. Risk difference (CI) for 10 mg is 1.2 (0.2, 2.5) and for 25 mg is 0.9 (0.2, 2.0)
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Elevated transaminases led to treatment interruption in one subject with maximum ALT >3x ULN and to treatment discontinuation in one subject with maximum AST >5x ULN, both receiving brensocatib 10 mg. Review of the AEs in subjects with elevated transaminases did not reveal other concomitant hepatobiliary AEs.

To complete the assessment for potential drug-induced hepatobiliary injury, the review team explored all subjects with hepatobiliary AEs (14). Among these 14 subjects, 2 subjects were in the 10-mg group, 11 subjects were in the 25-mg group, and 1 subject was in the placebo group. The most common AEs by PT were hepatic steatosis (1 subject in the 10-mg group, 4 subjects in the 25-mg group) and increased liver transaminases (3 subjects in the 25-mg group), none of which led to treatment interruption or discontinuation. Overall, review of the hepatobiliary events in combination with liver function analyte data did not reveal a concerning pattern of hepatobiliary injury.

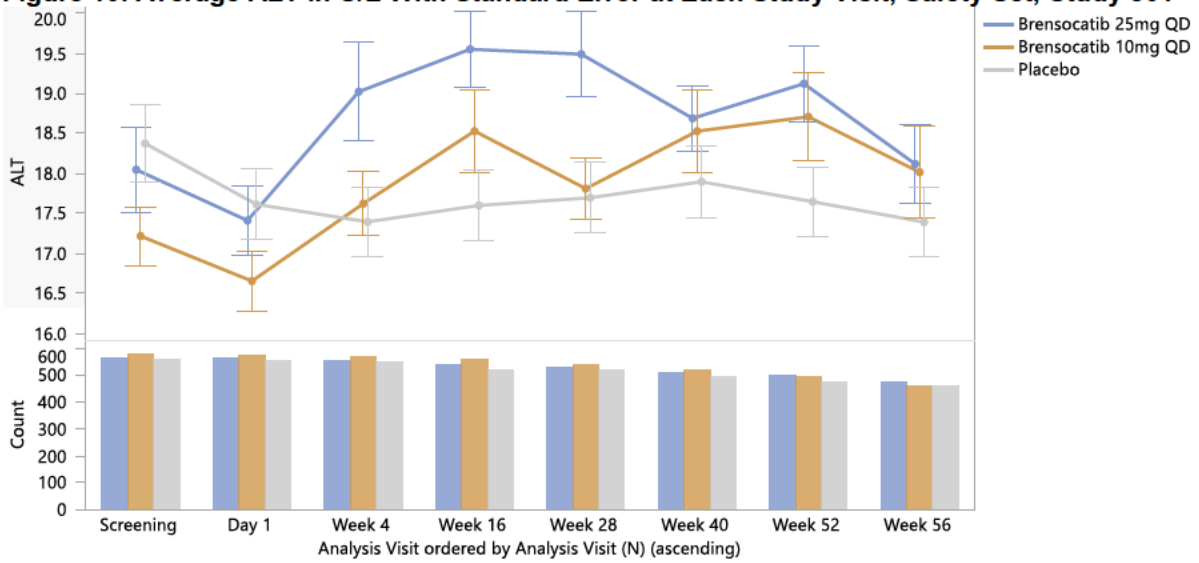
To explore the finding of increased transaminases further, we plotted the mean level of ALT, AST, and alkaline phosphatase at each study timepoint, shown in Figure 9, Figure 10 and Figure 11, respectively.

Figure 9. Average AST in U/L With Standard Error at Each Study Visit, Safety Set, Study 301



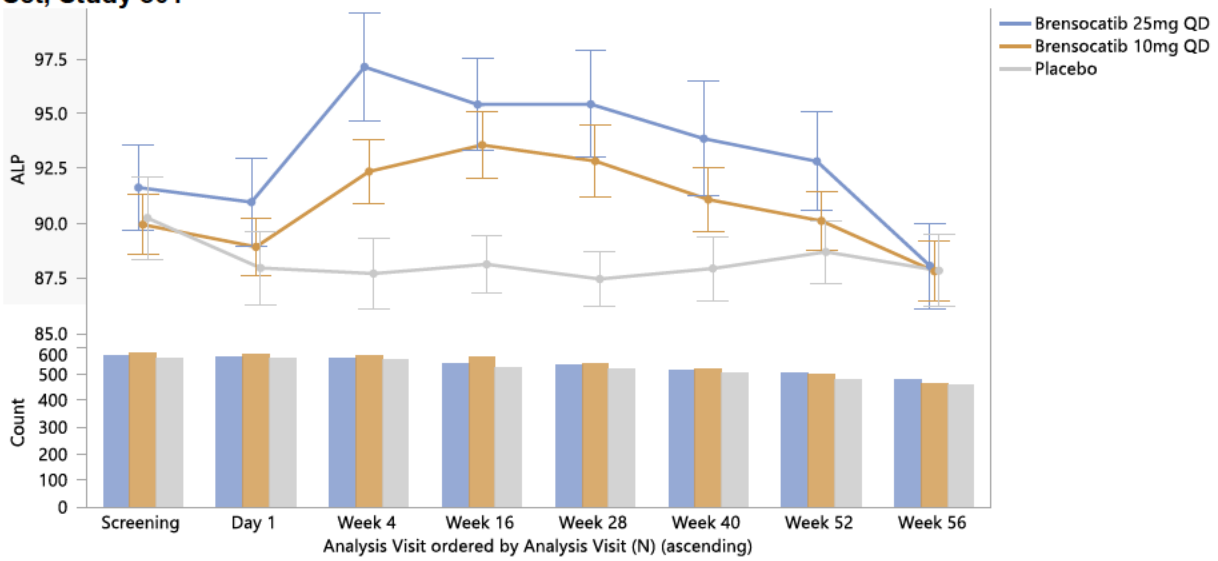
Source: adlb.xpt; Software: JMP Clinical 8.1
Duration is 52 weeks.
Count is number of subjects with data point at each study visit.
Abbreviations: AST, aspartate aminotransferase; QD, once daily; U/L, units per liter

Figure 10. Average ALT in U/L With Standard Error at Each Study Visit, Safety Set, Study 301



Source: adlb.xpt; Software: JMP Clinical 8.1
Duration is 52 weeks.
Count is number of subjects with data point at each study visit.
Abbreviations: ALT, alanine aminotransferase; QD, once daily; U/L, units per liter

Figure 11. Average Alkaline Phosphatase in U/L With Standard Error at Each Study Visit, Safety Set, Study 301



Source: adlb.xpt; Software: JMP Clinical 8.1
Duration is 52 weeks.
Count is number of subjects with data point at each study visit.
Abbreviations: ALP, alkaline phosphatase; QD, once daily; U/L, units per liter

For completeness, we also plotted the mean total bilirubin level at each study time point, and no meaningful difference was observed, consistent with the findings from Table 35. In general, across all study visits beginning at Week 4 through Week 52, there was an observed increase from Baseline in average ALT, AST, and alkaline phosphatase levels in both brensocatib groups compared to the placebo with minimal to no overlap of standard error bars observed for ALT and alkaline phosphatase. A greater increase was observed in the brensocatib 25-mg group relative to the 10-mg group across all three analytes at all time points, though notably there is significant overlap between the standard error bars. Averages returned to baseline across all analytes at the Week 56 visit, which corresponds with the 4-week follow-up visit after completion of the treatment period, suggesting the effect is related to brensocatib treatment.

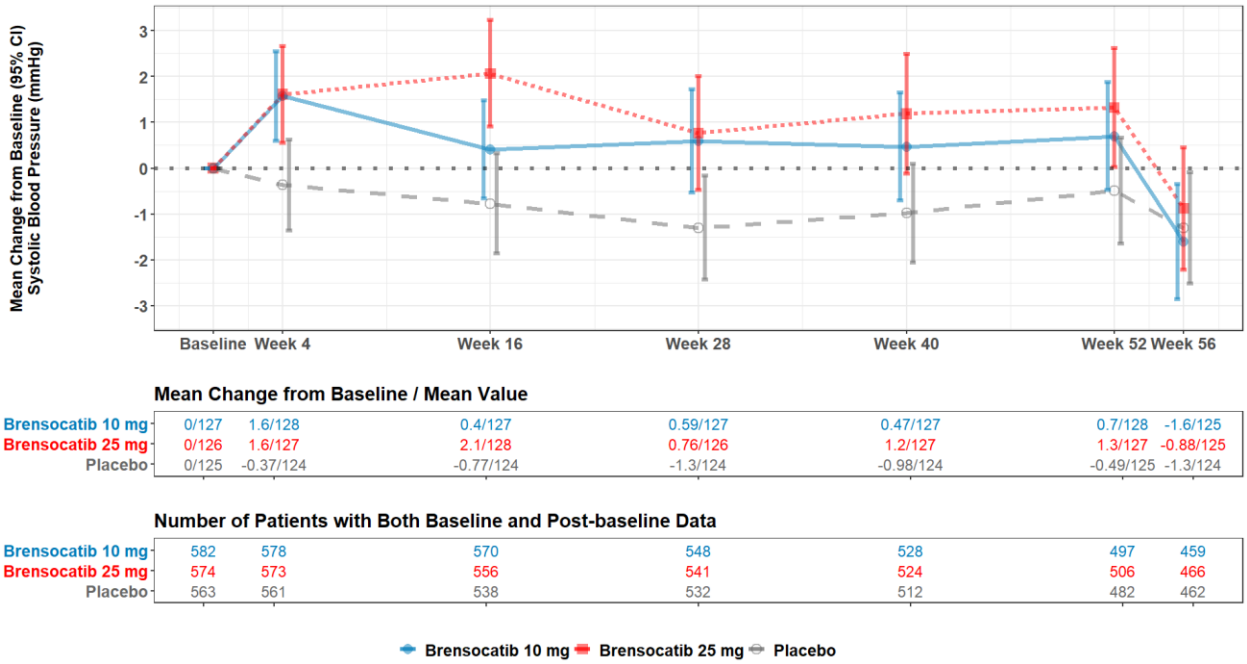
In summary, DILI was not observed in Study 301; however, we observed a small number of subjects meeting criteria for Temple's Corollary and an average increase from baseline in the liver biochemistry analytes alkaline phosphatase, ALT, and AST while on treatment. There were a small number of hepatobiliary AEs (0.8% total population), which occurred in the absence of concomitant liver analyte abnormalities. Although these data alone are not sufficient to suggest an increased risk for DILI, the observed increases in liver biochemistry will be important to communicate in the USPI to prescribers who manage patients with NCFB in combination with other comorbidities and concomitant medications (see Section 23). Monitoring of these signals in the post-market setting is appropriate through routine pharmacovigilance.

7.6.1.9. Vital-Sign Analyses, Study 301

No clinically significant changes in mean values over time and shift analysis were observed for diastolic blood pressure, heart rate, and respiratory rate. Review of systolic blood pressure data demonstrated a mean increase from baseline during the treatment period for subjects in the brensocatib groups compared to placebo (see Figure 12). Aside from a small difference at

Week 16 between brensocatib 25 mg and placebo, the CI error bars mostly overlap, indicating most differences may not be clinically meaningful.

Figure 12. Mean Systolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Study 301



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Abbreviation: CI, confidence interval

This review of systolic blood pressure data did not identify additional information about the risks for increases in blood pressure. However, since hypertension occurred at a greater frequency within the brensocatib 10-mg group (see Table 30), it will be listed in the adverse reactions table of the USPI.

7.6.1.10. Subgroup Analyses, Study 301

In general, there were no clinically meaningful differences in the frequency of AEs by demographic factors of sex, age, race, and ethnicity or by baseline disease characteristics of bronchiectasis etiology, BSI score, *P. aeruginosa* positivity, and number of pulmonary exacerbations in the last year (data not shown). Safety analyses by subgroup and dose level are further discussed under the key safety review issue of Dose Selection in Section 7.7.1.

Study 301 enrolled 41 adolescents who demonstrated comparable efficacy and PK responses consistent with the overall population (Section 6.3.2). Adolescent safety analyses were performed to identify any safety signals that may be unique to this population and to evaluate whether the benefit-risk of brensocatib 10 mg or 25 mg would be more appropriate for adolescents because of different safety profiles.

Among the 41 adolescents, 31 experienced a TEAE. The incidence of TEAEs among adolescents was generally balanced across treatment groups, with 82%, 63%, and 88% occurring in the

brensocatib 10 mg, 25 mg, and placebo groups, respectively. Most of these events were mild (71%) or moderate (34%) and were comparably distributed across the entire age range of 12- to 17-year-old subjects. One subject discontinued treatment and the study due to the AE of nausea in the 25-mg group.

There were no deaths. Seven SAEs occurred in five adolescents affecting 1, 3, and 5subjects in the brensocatib 10 mg, 25 mg, and placebo groups, respectively. Reported SAEs include bronchiectasis (n=3), *Pseudomonas* infection (n=2), pneumonia (n=1), and viral pharyngitis and are reflective of the sequelae of NCFB and consistent with the distribution of SAEs observed in the total population (refer to Table 27). Review of the AESIs identified one event each of hyperkeratosis (10 mg), gingival disorder (25 mg), and pneumonia (25 mg) in the adolescent subgroup. There were no AESIs of severe infection meeting the protocol definition (Section 17). Although there were three reported gingival disorder AEs (Table 36), only one met the criteria of clinically defined periodontal disease per dentist/periodontist assessment (Section 17).

Table 36. Treatment-Emergent Adverse Events by Preferred Term Occurring in Two or More Adolescent Subjects, Study 301

Preferred Term	Brensocatib 10 mg (N=17)	Brensocatib 25 mg (N=16)	Placebo (N=8)
Headache	2 (11.8)	2 (12.5)	1 (12.5)
Bronchiectasis	0	2 (12.5)	1 (12.5)
Gingival disorder	1 (5.9)	2 (12.5)	0
Nasopharyngitis	1 (5.9)	0	2 (25.0)
Upper respiratory tract infection	2 (11.8)	1 (6.2)	0
Diarrhea	2 (11.8)	0	0
Gastroenteritis	0	2 (12.5)	0
Skin lesion	0	2 (12.5)	0
Viral infection	0	2 (12.5)	0
Viral pharyngitis	2 (11.8)	0	0

Source: Clinical Reviewer calculated in OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AGEGR1 = '12 to <18 years'.
Rows - Dataset: Adverse Events; Filter: SAFFL = 'Y', TRTEMFL = 'Y'
Abbreviations: N, number of subjects; QD, once daily; TEAE, treatment-emergent adverse event

The most common TEAEs observed among adolescents are presented in Table 36. The TEAEs that occurred more in brensocatib-treated adolescents compared to placebo-treated adolescents were either balanced between treatment arms (i.e., viral and gastrointestinal TEAEs), associated with NCFB disease (i.e., bronchiectasis), or consistent with the adverse reactions in the total population presented in Table 30 (headache, upper respiratory tract infection, and skin lesion). Although Table 36 demonstrates a dose-dependent increase in gingival disorders, review of all gingival and periodontal terms used for this AESI in the total population (see Section 7.6.1.6) found a comparable frequency of 12.5% across all treatment arms (2 subjects in 10-mg group, 2 subjects in 25-mg group, and 1 subject in placebo group).

The adolescent safety database is limited by the overall small sample size, in part because the primary database lock occurred while 20 subjects remained on treatment. Review of the 120-day safety update, which included follow-up information on these subjects and is discussed in Section 17, did not reveal new or different information regarding risks in adolescents. Overall, the safety profile in adolescents appears consistent with the overall population. There were no meaningful dose-dependent differences observed to suggest either dose is more appropriate in

this population based on the safety profiles. Refer to Section 6.3.2 for additional discussion of the benefit-risk assessment in adolescents. Monitoring of safety in the post-market setting is appropriate through routine pharmacovigilance. (see Section 23).

7.6.2. Safety Results, Study 201

7.6.2.1. Overview of Adverse Events Summary, Study 201

The overview of AEs for Study 201 is found in Table 37. The overall frequency of reported TEAEs was higher in the brensocatib groups (92.6%, 10 mg and 83.1%, 25 mg) compared to placebo (78.8%). As in Study 301, most of the reported AEs were mild to moderate in severity, and the frequency of reported SAEs was higher in the placebo group (22.4%) compared to the brensocatib groups (13.6%, 10 mg and 11.2%, 25 mg). There was also a slightly higher frequency of AEs leading to discontinuation of study drug in the placebo group compared to the brensocatib groups (10.6% compared to 7.4% and 6.7% in the 10-mg and 25-mg groups, respectively).

Table 37. Overview of Adverse Events, Safety Population, Study 201

Event Category	Brensocatib 10 mg N=81 n(%)	Brensocatib 25 mg N=89 n(%)	Placebo N=85 n(%)
SAE	11 (13.6)	10 (11.2)	19 (22.4)
SAEs with fatal outcome	0	1 (1.1)	0
Life-threatening SAEs	1 (1.2)	0	0
SAEs requiring hospitalization	11 (13.6)	10 (11.2)	18 (21.2)
SAEs resulting in disruption of normal life functions	1 (1.2)	0	0
Other	2 (2.5)	0	1 (1.2)
AE leading to permanent discontinuation of study drug	6 (7.4)	6 (6.7)	9 (10.6)
AE leading to dose modification of study drug	6 (7.4)	7 (7.9)	5 (5.9)
AE leading to interruption of study drug	6 (7.4)	7 (7.9)	5 (5.9)
Any AE	75 (92.6)	74 (83.1)	67 (78.8)
Severe and worse	4 (4.9)	7 (7.9)	13 (15.3)
Moderate	44 (54.3)	37 (41.6)	33 (38.8)
Mild	27 (33.3)	30 (33.7)	21 (24.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as preexisting AEs that worsen in severity after the first administration of study drug or AEs that have onset on or after the first administration of study drug through 30 days after the last administration of study drug. Duration is 24 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Study 201

There was one death reported in Study 201 as shown in Table 37. The subject was a 67-year-old white female treated with brensocatib 25 mg, and the death was from respiratory failure deemed related to progression of underlying bronchiectasis. This single event is consistent with the observed AEs leading to death in Study 301 and does not raise any additional safety concerns.

7.6.2.3. Serious Adverse Events, Study 201

A total of 40 (15.7%) subjects experienced at least one SAE as shown in Table 38. Most SAEs occurring in more than one subject had a 95% CI for the risk difference that included the null between placebo and either brensocatib treatment groups.

Table 38. Serious Adverse Events by Preferred Term Occurring in More Than Two Subjects, Safety Population, Study 201

Preferred Term	Brensocatib 10 mg N=81 n(%)	Brensocatib 25 mg N=89 n(%)	Placebo N=85 n(%)
Any SAE	11 (13.6)	10 (11.2)	19 (22.4)
Pneumonia	0	4 (4.5)	3 (3.5)
Infective exacerbation of bronchiectasis	5 (6.2)	4 (4.5)	9 (10.6)
Hemoptysis	0	0	2 (2.4)

Source: adae.xpt; Software: R
Duration is 24 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event.

As in Study 301, the most frequently reported SAE was infective exacerbation of bronchiectasis, which occurred with higher frequency in the placebo group (10.6%) compared to both brensocatib groups (6.2% and 4.5% in the 10-mg and 25-mg groups, respectively) consistent with the overall treatment effect of brensocatib. Overall, the analysis of the SAEs did not raise any additional safety concerns.

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, Study 201

A total of 21 (8.2%) subjects discontinued treatment due to an AE. A greater frequency of subjects in the placebo group (10.6%) discontinued due to an AE compared to both brensocatib groups (7.4% and 6.7% in 10-mg dose and 25-mg dose group, respectively). There was no consistency in the AEs leading to discontinuation, and most AEs occurred in one subject with the exclusion of pneumonia, which occurred in two subjects in the placebo group, and headache, which occurred in two subjects in the brensocatib 25-mg dose group. These data are consistent with the observed treatment discontinuations due to an AE in Study 301.

7.6.2.5. Treatment-Emergent Adverse Events, Study 201

A total of 216 (84.7%) subjects experienced at least one TEAE during the 24-week treatment period. A summary of TEAEs occurring in ≥2% frequency in any treatment arm is displayed in Table 39.

Table 39. Treatment-Emergent Adverse Events by Preferred Term Occurring at ≥2% Frequency, Safety Population, Study 201

Preferred Term	Brensocatib 10 mg N=81 n(%)	Brensocatib 25 mg N=89 n(%)	Placebo N=85 n(%)
Any AE	75 (92.6)	74 (83.1)	67 (78.8)
Cough	15 (18.5)	12 (13.5)	10 (11.8)
Sputum increased	9 (11.1)	9 (10.1)	6 (7.1)
Headache	8 (9.9)	12 (13.5)*	3 (3.5)
Infective exacerbation of bronchiectasis	5 (6.2)	4 (4.5)	9 (10.6)
Diarrhea	5 (6.2)	3 (3.4)	9 (10.6)
Fatigue	3 (3.7)	7 (7.9)	6 (7.1)
Sinusitis	5 (6.2)	4 (4.5)	6 (7.1)
Dyspnea	3 (3.7)	9 (0.1)*	2 (2.4)
Upper respiratory tract infection	6 (7.4)	4 (4.5)	4 (4.7)
Dry skin	2 (2.5)	4 (4.5)	4 (4.7)
Hemoptysis	6 (7.4)	2 (2.2)	2 (2.4)
Pyrexia	4 (4.9)	4 (4.5)	2 (2.4)
Nasopharyngitis	4 (4.9)	2 (2.2)	3 (3.5)
Pneumonia	1 (1.2)	5 (5.6)	3 (3.5)
Urinary tract infection	2 (2.5)	3 (3.4)	4 (4.7)
Arthralgia	6 (7.4)*	1 (1.1)	1 (1.2)
Dizziness	2 (2.5)	3 (3.4)	3 (3.5)
Hypertension	2 (2.5)	1 (1.1)	5 (5.9)
Nausea	3 (3.7)	1 (1.1)	4 (4.7)
Vertigo	2 (2.5)	2 (2.2)	4 (4.7)
Constipation	2 (2.5)	2 (2.2)	3 (3.5)
Oropharyngeal pain	2 (2.5)	3 (3.4)	2 (2.4)
Periodontal disease	2 (2.5)	5 (5.6)*	0
Tooth fracture	4 (4.9)	1 (1.1)	2 (2.4)
Abdominal pain upper	3 (3.7)	0	3 (3.5)
Back pain	1 (1.2)	2 (2.2)	3 (3.5)
Bronchitis	4 (4.9)	1 (1.1)	1 (1.2)
Increased appetite	3 (3.7)	2 (2.2)	1 (1.2)
Muscle spasms	3 (3.7)	1 (1.1)	2 (2.4)
Pain in extremity	2 (2.5)	1 (1.1)	3 (3.5)
Rash	3 (3.7)	1 (1.1)	2 (2.4)
Vomiting	2 (2.5)	1 (1.1)	3 (3.5)
Chest discomfort	1 (1.2)	4 (4.5)	0
Dysphonia	1 (1.2)	2 (2.2)	2 (2.4)
Epistaxis	1 (1.2)	3 (3.4)	1 (1.2)
Hyperkeratosis	3 (3.7)	1 (1.1)	1 (1.2)
Influenza	1 (1.2)	0	4 (4.7)
Lower respiratory tract infection	1 (1.2)	3 (3.4)	1 (1.2)
Pruritus	1 (1.2)	3 (3.4)	1 (1.2)
Respiratory tract congestion	2 (2.5)	0	3 (3.5)
Skin abrasion	2 (2.5)	2 (2.2)	1 (1.2)
Skin lesion	1 (1.2)	3 (3.4)	1 (1.2)
Wheezing	2 (2.5)	2 (2.2)	1 (1.2)

Source: adae.xpt; Software: R
Duration is 24 weeks.
* Higher risk difference with 95% confidence interval (CI) between total treatment and comparator where CI excludes zero occurred in the 25-mg group for headache [10.0 (1.8,19.1)], dyspnea [7.8 (0.6, 1.6)], and periodontal disease [5.6 (1.2, 12.5)] and in the 10-mg group for arthralgia [6.2 (0.1, 14.2)].
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

The most common AEs were cough, sputum increased, headache, and infective exacerbation of bronchiectasis. Adverse events that occurred with greater frequency in the brensocatib 25-mg group compared to the placebo group with 95% CI of the risk difference excluding the null included headache (13.5% and 3.5%), dyspnea (10.1% and 2.4%), periodontal disease (5.6% and 0%), and chest discomfort (4.5% and 0%). A greater frequency of arthralgia was reported in the brensocatib 10-mg group compared to the placebo group (7.4% and 1.2%), with 95% CI of the risk difference excluding the null. Cough, increased sputum, dyspnea, and chest discomfort are common symptoms in patients with bronchiectasis and were also common AEs reported in Study 301, where the risk difference 95% CI excluded the null. As in Study 301, the frequency of headache and periodontal disease occurred with higher frequency in the brensocatib treatment groups, with headache occurring in a dose-dependent fashion. Overall, the review of the TEAEs from Study 201 is consistent with the observations from Study 301 and does not reveal any new safety concerns.

7.6.2.6. Adverse Events of Special Interest, Study 201

The Applicant pre-defined infections, skin-related events, and dental-related events as AESIs for Study 201. There were no clinically meaningful differences in infection AESIs between study groups, with slightly higher frequency of reported AEs in the placebo group compared to brensocatib groups. Skin-related events were either mild or moderate in severity and occurred with greater frequency in the brensocatib treatment groups compared to placebo. There was a greater frequency of events occurring in the 25-mg group (23.6%) compared to the 10-mg group (14.8%) consistent with the observed trends in Study 301.

Applicant-defined dental-related AESIs were more frequent (25 subjects, 9.8% total population) in Study 201 compared to Study 301 (Section 7.6.1.6), and the majority of events occurred in the brensocatib groups (13 subjects, 16% in 10 mg and 9 subjects, 10% in 25 mg) compared to placebo (3 subjects, 3.5%). Study 201 employed a broader grouping of terms for the assessment of this AESI compared to Study 301, in which the custom query was narrowed, based on findings from Study 201. Therefore, to compare the frequency of events between trials more accurately, we reanalyzed Study 201 data using the grouping of PTs for this AESI in Study 301. That analysis is displayed in Table 40.

Table 40. Dental AESIs by Preferred Term, Safety Population, Study 201

Preferred Term	Brensocatib 10 mg N=81 n(%)	Brensocatib 25 mg N=89 n(%)	Placebo N=85 n(%)
Number of subjects with at least 1 dental event	8 (9.9)*	9 (10.1)*	2 (2.4)
Gingival bleeding	1 (1.2)	0	0
Gingival discomfort	1 (1.2)	0	0
Gingival disorder	1 (1.2)	0	0
Gingival pain	0	3 (3.4)	0
Gingival recession	1 (1.2)	0	0
Gingivitis	0	1 (1.1)	0
Noninfective gingivitis	0	0	1 (1.2)
Oral pain	1 (1.2)	0	0

Preferred Term	Brensocatib 10 mg N=81 n(%)	Brensocatib 25 mg N=89 n(%)	Placebo N=85 n(%)
Periodontal disease	2 (2.5)	5 (5.6)*	0
Periodontitis	1 (1.2)	0	1 (1.2)

Source: adae.xpt; Software: R
Duration is 24 weeks.
Asterisk (*) indicates that 95% confidence interval for the Risk Difference vs placebo excludes the null.
Risk difference value for periodontal disease is 5.6 (CI 1.2, 12.5) in 25-mg group.
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

In total, both brensocatib groups had generally comparable frequencies of total dental events and comparable increased risk differences with confidence intervals excluding the null for both doses compared to placebo. The most frequently reported terms were periodontal disease and gingival pain, and the majority of events were mild (n = 16) or moderate (n = 3) in severity. Periodontal disease demonstrated a dose-dependent distribution with the 25-mg group having an increased risk difference versus placebo with a confidence interval that excluded the null.

Study 201 utilized a more enhanced monitoring program for the evaluation of dental events compared to Study 301 as discussed in Sections 7.6.1.6, 15.1.3.2, and 15.2.3.2. The differences in monitoring may have resulted in underreporting of events in Study 301. The more robust monitoring conducted in all subjects irrespective of signs or symptoms suggests that the frequency of dental events and dose-dependent distribution of periodontal disease in Study 201 may better reflect the gingival/periodontal effects of brensocatib treatment. As a result, the dental findings in Study 201 will be documented in Adverse Reactions, and gingival and periodontal adverse events will be included as a Warning and Precaution in the label to provide actionable guidance; although most events were mild in severity, the data suggest that assessment by a dentist may improve recognition—thereby treatment—of periodontal and gingival adverse effects of brensocatib. See Section 23 for labeling recommendations. A PMR/postmarketing commitment is not required given the predominately mild intensity and overall low incidence. Monitoring through routine pharmacovigilance may further elucidate the gingival/periodontal incidence and effects of long-term brensocatib treatment in the postmarket setting.

7.6.2.7. Laboratory Findings, Study 201

As with Study 301, the Applicant conducted analyses of clinical laboratory results including chemistry and hematologic parameters in Study 201. Analyses included the changes in mean values over time, changes in individual subjects over time, and potentially clinically significant values. There were no apparent clinically meaningful trends or mean changes from baseline observed in any hematologic or chemistry parameters. Potentially clinically significant values were infrequently observed and generally balanced between groups. As noted in Section 7.6.1.7, Study 201 did not find a greater frequency of high bicarbonate values (exceeding 30 mEq/L) in brensocatib groups compared to placebo, and in fact, the trend was in the opposite direction with higher frequency in the placebo group.

7.6.2.8. Assessment of Drug-Induced Liver Injury, Study 201

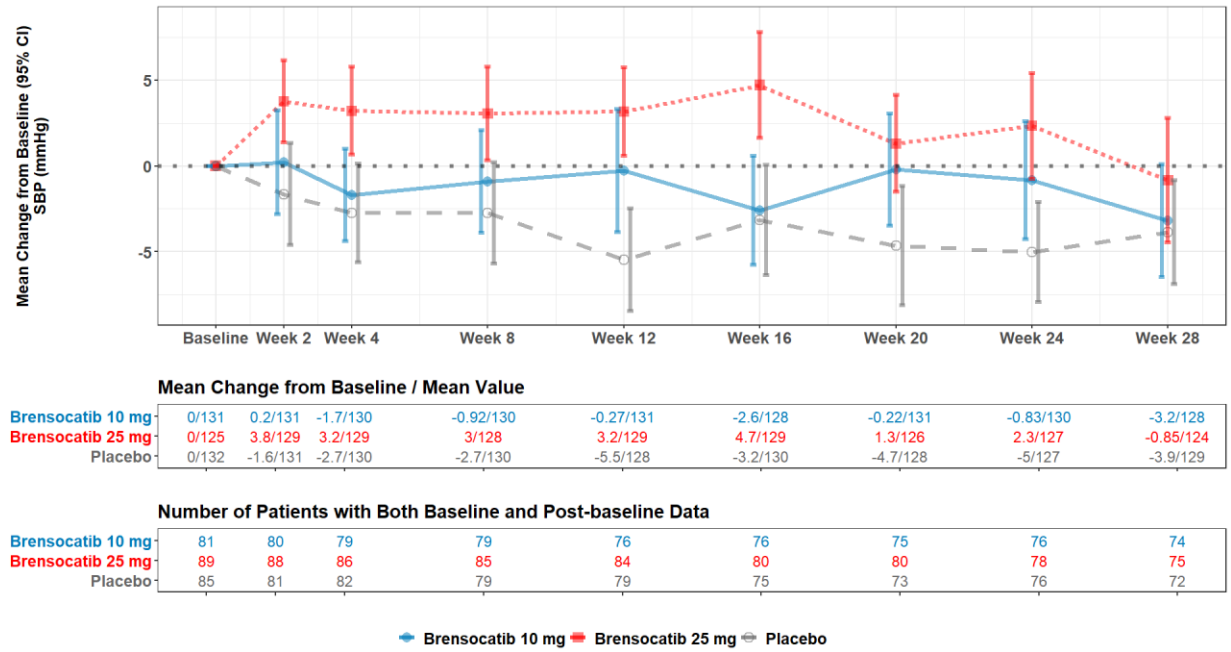
The screening assessment for potential cases of serious DILI did not identify any cases of potential Hy's Law. There were two Temple's corollary cases in subjects who received brensocatib, one in each dose group. The review of liver biochemistry analyte data from Study 201 was notable for 2 cases of ALT elevation >3x ULN, 1 from each brensocatib treatment group, and 1 case of AST elevations >3x ULN in the brensocatib 10 mg treatment group. There were a few observed high alkaline phosphatase levels, but the increases were balanced across groups. There were no observed increases (>1.5X ULN) in total bilirubin in any group. None of the elevations in ALT, AST, or alkaline phosphatase resulted in treatment withdrawal or discontinuation nor were they associated with hepatobiliary AEs. Overall, the assessment of DILI from Study 201 did not identify concerns for liver injury or affect the interpretation of the safety review findings of Study 301.

7.6.2.9. Vital-Sign Analyses, Study 201

There were no clinically meaningful differences between groups in maximum systolic blood pressure, maximum diastolic blood pressure, or hypotension. No significant changes in mean values over time and shift analysis were observed for diastolic blood pressure, heart rate, and respiratory rate.

As in Study 301, review of the mean systolic blood pressure changes from baseline across the treatment period of Study 201 shows an elevation in SBP in the brensocatib groups overtime and, in particular at Week 16 for the brensocatib 25-mg group. This is displayed graphically in Figure 13.

Figure 13. Mean Systolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Study 201



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Abbreviations: CI, confidence interval; SBP, systolic blood pressure

Aside from a small difference at Week 16 between brensocatib 25-mg group and placebo, the CI error bars mostly overlap, indicating most differences may not be clinically meaningful.

Overall, the vital sign data from Study 201 does not raise any safety concerns, and the nominal increase systolic blood pressure in the treatment arms supports the observations in Study 301.

7.6.2.10. Subgroup Analyses, Study 201

Safety analyses were conducted based on demographic and baseline characteristic subgroupings that are discussed in further detail in Section 7.7.1. Although no differences were observed across these subgroupings in the safety analyses of pooled trial data, analysis of the key demographic subgroups for Study 201 found a greater frequency of overall TEAEs in the brensocatib 10-mg dose group compared to placebo for males (96% versus 71%) with a risk difference CI excluding the null. There was also a higher frequency in TEAEs for individuals ≥55 years in the brensocatib 10-mg dose group compared to placebo (93.8% versus 78.3%), but the frequency was more balanced in those under 55 years of age. Higher frequencies of TEAEs were also seen in White, non-Hispanic, and those subjects outside of the USA; however, most of the subjects in this trial fall into those categories and therefore interpretation is limited. Although higher frequencies of overall TEAEs were observed, there were no clear trends by system organ class or PT. Furthermore, similar subgroup analyses performed in Study 301 (Section 7.6.1.10) did not reveal clinically meaningful differences between subgroups in overall frequency of TEAEs. These findings for Study 201 are small differences and their interpretation is limited by the trial sample size and duration.

7.7. Key Safety Review Issues

7.7.1. Dose Selection

Issue

The Applicant has submitted data from two clinical trials evaluating the efficacy and safety of brensocatib 10 mg and 25 mg versus placebo. Refer to Section 6.3.1 for discussion of the comparative efficacy of each dose to support marketing.

Background

As discussed in Section 6.3.1, the Applicant initially proposed marketing the 25-mg dose only based on Study 301 efficacy data for post-BD FEV1 and the QoL-B RSS. This review found comparable efficacy with minimal difference in treatment effects between the 10-mg and 25-mg doses. Thus, we explored the safety database to evaluate whether there were differences in safety that could inform the benefit-risk considerations between doses.

Assessment

Since both doses appear to be equally efficacious, we performed additional safety analyses to better understand these signals and to explore whether specific subgroups may benefit from better tolerability with the 10-mg dose versus the 25-mg. These analyses looked at the frequency of these events by sex, race, past history of smoking, underlying bronchiectasis etiology, baseline NCFB characteristics (e.g., BSI score, *P. aeruginosa* positivity, number of pulmonary exacerbations in the last year), and concomitant medications. Furthermore, we performed time-to-event analyses among the predefined AESIs to gain insight into whether some toxicities may be time-dependent. Together, these analyses aimed to inform the benefit-risk considerations of both doses, to investigate whether one or more subpopulations would be more appropriate for a specific dose for safety reasons, and whether there were data to support a 'starting' dose or dose escalation approach (acknowledging Studies 301 and 201 were not designed to assess that).

Subpopulation Analyses

Analysis of safety data from Study 301 and Study 201 demonstrates both the 10-mg and 25-mg doses have generally comparable safety profiles with dose-dependent (10 mg <25 mg) effects observed among a limited number of adverse reactions including upper respiratory tract infections, headache, herpes zoster, and skin-related events.

Small dose-dependent imbalances were observed with herpes zoster infection, most commonly among adults aged 65 and older, a finding consistent with the epidemiology of herpes zoster. Otherwise, no other trends were observed in the remaining subpopulation analyses.

When analyzed by the subgroups listed above, no trends across individual subpopulations were observed for the PTs of upper respiratory tract infections, headache, and skin related events. Overall, analyses by sex, race, past history of smoking, underlying bronchiectasis etiology, baseline NCFB characteristics, and concomitant medications did not reveal meaningful trends to suggest any of these factors to be suitable predictors of tolerability or increased risk (data not shown). Refer also to Sections 7.6.1.10 and 7.6.2.10 for additional discussion of subgroups.

Time-to-Event Analyses

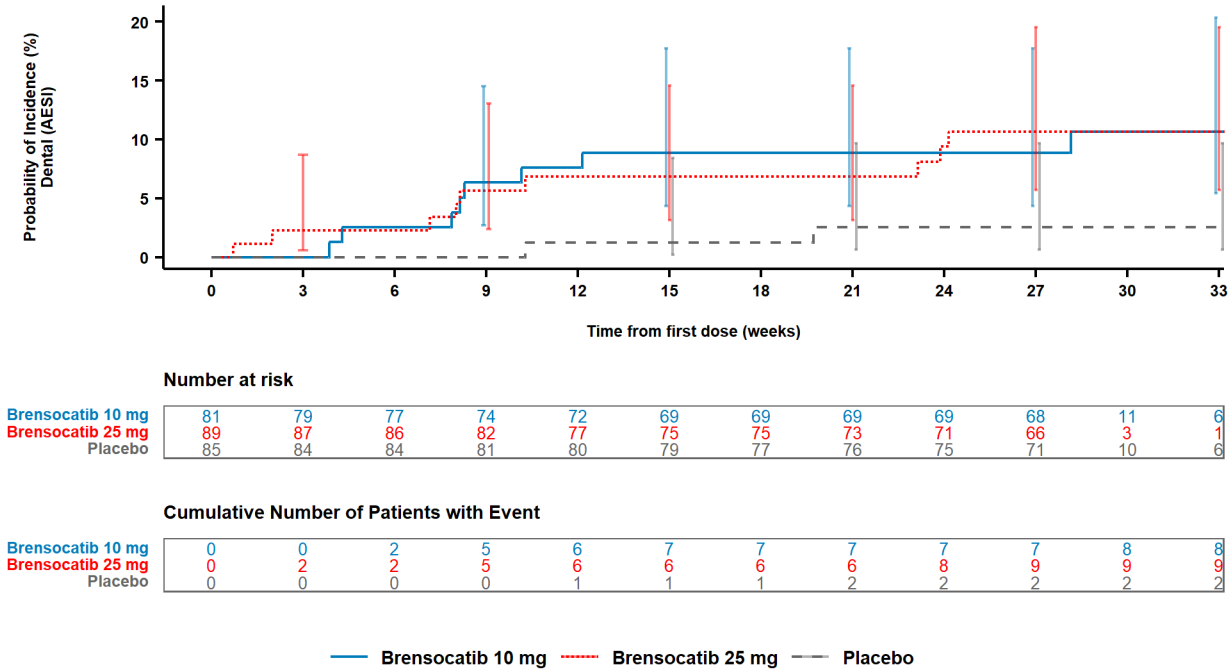
Time-to-event analyses were conducted for the predefined AESIs of hyperkeratosis, gingival/periodontal disease, pneumonia, and other severe infections (Study 301) and for skin, dental, and infection (Study 201) to evaluate for differences in the timing of onset between the 10-mg and 25-mg doses. The goal of these analyses was to investigate if a relationship existed between dose and timing of events to explore whether rapid escalation of dose would result in quicker time to onset of toxicities. No differences were observed for pneumonia and other severe infections (Study 301) or for infection (Study 201).

Gingival/Periodontal and Dental Events

The analysis for gingival/periodontal events in Study 301 demonstrated separation of the curves between brensocatib doses with 25-mg dose demonstrating a greater rate of accumulation around Week 20 (Day 80). However, the 25-mg group approximated the placebo group for the duration of the treatment period and the confidence intervals for all treatment groups overlapped substantially. Conversely, time-to-event analysis with the Applicant-defined dental AESI grouping in Study 201 demonstrated separation of the curves across all treatment groups with a greater rate of initial increase in the brensocatib groups (25 mg >10 mg) compared to placebo.

As discussed in Sections 7.6.1.6 and 7.6.2.6, because the trials employed different assessment strategies for the evaluation of gingival/periodontal (Section 15.1.3.2) and dental (Section 15.2.3.2) events that likely contributed to differences in the reported frequencies of these events across trials, Study 201 data was filtered and reanalyzed to better compare against Study 301. Discussion of the results of this analysis are discussed in Section 7.6.2.6. As part of that additional analysis, a time-to-event assessment was performed and is displayed graphically in Figure 14.

Figure 14. Time to Onset of Dental AESI, Safety Population, Study 201



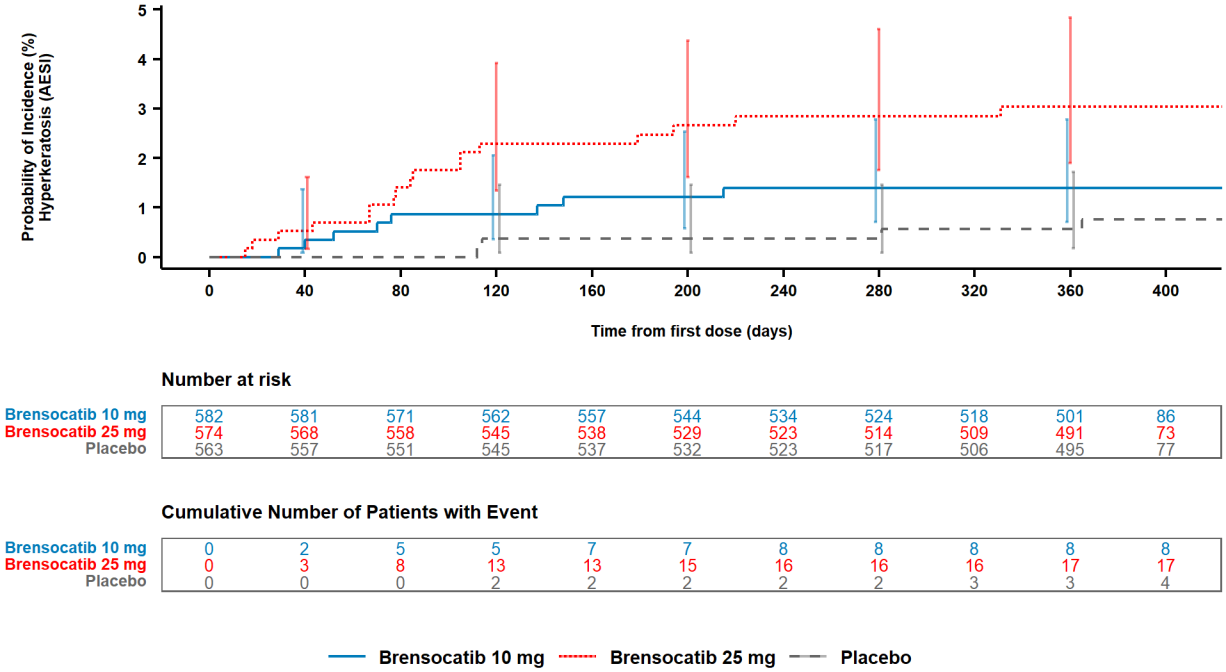
Source: adsl.xpt and adae.xpt; Software: R
Duration is 24 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviation: AESI, adverse event of special interest

There is an early small increase in dental events within the first 4 weeks of treatment in the 25-mg group with no overlap of confidence intervals. After Week 4, the curves for both the 10-mg and 25-mg groups approximate one another for the remainder of the treatment period. This suggests a possible increased risk of early-onset dental adverse events with the higher dose. These results in the gingival/periodontal and dental analysis provide additional evidence supporting the option of a lower dose of comparable efficacy; (b) (4) (b) (4).

Hyperkeratosis and Skin Events

The analysis for hyperkeratosis and skin events demonstrated separation of the curves across treatment arms in both trials and are displayed graphically in Figure 15 (Study 301) and Figure 16 (Study 201).

Figure 15. Time to Onset of Hyperkeratosis AESI, Safety Population, Study 301



Number at risk

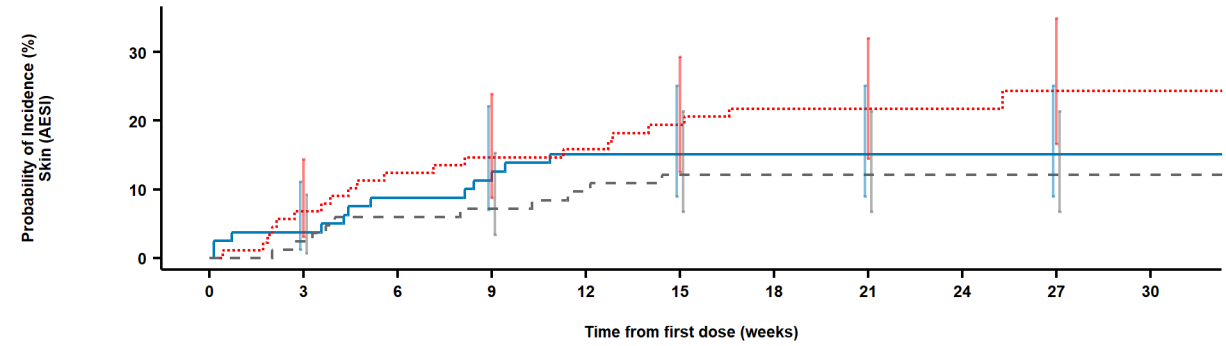
Brensocatib 10 mg	582	581	571	562	557	544	534	524	518	501	86
Brensocatib 25 mg	574	568	558	545	538	529	523	514	509	491	73
Placebo	563	557	551	545	537	532	523	517	506	495	77

Cumulative Number of Patients with Event

Brensocatib 10 mg	0	2	5	5	7	7	8	8	8	8	8
Brensocatib 25 mg	0	3	8	13	13	15	16	16	16	17	17
Placebo	0	0	0	2	2	2	2	2	3	3	4

Source: adae.xpt; Software: R
Duration is 52 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviation: AESI, adverse event of special interest

Figure 16. Time to Onset of Hyperkeratosis AESI, Safety Population, Study 201



Number at risk

Brensocatib 10 mg	81	76	72	70	66	65	65	65	65	64	8
Brensocatib 25 mg	89	83	77	74	72	67	65	63	63	57	3
Placebo	85	82	79	75	73	71	69	69	69	65	10

Cumulative Number of Patients with Event

Brensocatib 10 mg	0	3	7	10	12	12	12	12	12	12	12
Brensocatib 25 mg	0	6	11	13	14	17	19	19	19	21	21
Placebo	0	2	5	6	8	10	10	10	10	10	10

Source: adsl.xpt and adae.xpt; Software: R
Duration is 24 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviation: AESI, adverse events of special interest

Hyperkeratosis events occurred earlier following treatment initiation in the 25-mg group and continued to accumulate over time at a faster rate compared to subjects in the 10-mg and placebo groups. Although significant overlap exists in the confidence intervals between the 10-mg and 25-mg groups across all time points, the confidence intervals for the 25-mg group no longer overlap with the placebo group beginning at Day 200 (Week 28) and remain separated for the duration of the treatment period. Time-to-event analysis of hyperkeratosis events in Study 201 demonstrate a similar though less impressive pattern of separation that may be reflective of a smaller population size and shorter treatment duration, which collectively may not have been sufficient to detect a difference. Although time-to-event analyses were not performed for all observed dose-dependent AEs due to the small number of events in each group, these results in the hyperkeratosis analysis provide additional evidence supporting the option of providing a lower dose of comparable efficacy; (b) (4)

(b) (4)

Conclusion

Review of the safety data from Studies 301 and 201 reveals dose-dependent adverse reactions that support marketing of the 10-mg dose to have as an option for those patients who may experience tolerability issues on 25 mg. As discussed in Section 6.3.1, modest increases in post-BD FEV1 that were statistically significant were seen only for the 25-mg dose; in addition, most dose-dependent adverse reactions were mild to moderate in intensity and not serious, and no significant differences in AE-related drug discontinuations occurred (See Sections 7.6.1.4 and 7.6.2.4). These considerations taken together support marketing of both doses, rather than just the lower dose, to allow some patients the potential of additional benefit. Subgroup analyses did not identify variables to predict which populations may be at increased risk for adverse reactions or experience more severe adverse reactions. For these reasons and since there is insufficient efficacy data to support a specific starting dose, the recommended starting dose should be left to the discretion of the prescriber. Refer to Section 23 for additional labeling recommendations. See also Sections 6.3.1 and 7.6.1.10 for specific discussion of consideration of doses for adolescents.

7.7.2. Skin-Related Disorders

Issue

Review of safety data from Study 301 and Study 201 demonstrate dose-dependent increases in the AESI of hyperkeratosis as well as other skin-related adverse events, such as urticaria. The dose-dependent nature in combination with the potential for serious reactions and strong association with mechanism of action prompted the review team to examine this signal more closely and consider inclusion in the Warnings and Precautions section of the USPI with appropriate risk mitigation strategies.

Background

Papillon- Lefèvre Syndrome (PLS) is a clinical condition of DPP1 deficiency caused by biallelic loss-of-function variants in the gene *CTSC* (UniProt 2025). Patients with PLS develop a constellation of clinical manifestations among which diffuse palmoplantar hyperkeratosis, gingivitis, periodontal disease, and organ-specific infections are the most common and pathognomonic features (Almuneef et al. 2003; Ullbro et al. 2003; NORD 2019; OMIM 2025).

Other less common features include neoplasms affecting the skin, nail changes, hypertrichosis, and stomatitis (Gorlin et al. 1964; Murthy et al. 2005; Alsaif et al. 2019; NORD 2019; OMIM 2025). See Sections 7.2, 7.6.1.6, and 7.6.2.6 for additional information. These features informed the predefined AESIs. Review of the safety data from Studies 301 and 201 revealed dose-dependent adverse effects among several skin-related PTs, including hyperkeratosis, rash, urticaria, and neoplasms of the skin. The review team consulted DDD for expert review of the skin-related safety signals and for recommendations on appropriate labeling strategies.

Assessment

Hyperkeratosis and Other Non-neoplasm Skin Conditions

In the review of the safety databases of Study 301 and 201, hyperkeratosis, rash, and urticaria occurred with greater frequency in a dose-dependent fashion in the brensocatib treatment groups compared to placebo. These findings are summarized in Table 41 by both PT and Broad Food and Drug Administration Medical Dictionary for Regulatory Activities query (FMQ Broad) grouping.

Table 41. Summary of Skin-Related Events by Preferred Term and FMQ Broad, Studies 301 and 201, Safety Sets

	Study 301			Study 201		
Events	Brensocatib 10 mg (N=582) n(%)	Brensocatib 25 mg (N=574) n(%)	Placebo (N=563) n(%)	Brensocatib 10 mg (N=81) n(%)	Brensocatib 25 mg (N=89) n(%)	Placebo (N=85) n(%)
Preferred Term						
Hyperkeratosis	5 (0.9)	15 (2.6)	3 (0.5)	N/A	N/A	N/A
Rash	16 (2.7)	26 (4.5)	13 (2.3)	11 (13.6)	7 (7.9)	7 (8.2)
Urticaria	1 (0.2)	10 (1.7)	2 (0.4)	0	1 (1.1)	1(1.2)
FMQ Broad						
Rash	30 (5.2)	52 (9.1)	29 (5.2)	14 (17.3)	8 (9.0)	8 (9.4)
Urticaria	1 (0.2)	10 (1.7)	2 (0.4)	6 (7.4)	3 (3.4)	3 (3.5)

Source: Clinical Reviewer created table using Clinical Data Scientist outputs from adae.xpt, Software: R
Abbreviations: FMQ, FDA Medical Queries; N, number of subjects, n, number of subjects with specific event; N/A, not applicable.

In their consult memo addendum dated April 25, 2025, DDD noted that the pooled AE terms the Applicant used for "hyperkeratosis" were inappropriate as none of the pooled terms are consistent with hyperkeratosis. Some of the pooled terms, such as exfoliative rash, would be more appropriately grouped with other terms, in this case rash or dry skin. Therefore, to facilitate a more accurate review, DDD provided recommended groupings (refer to Section 17) of all skin-related PTs.

Table 42 displays the results of the grouped queries (GQs) and applicable PTs within a GQ that demonstrated increased risk differences where the CI excluded zero in one or more brensocatib treatment groups for Study 301.

Table 42. Summary of Skin-Related Events by Recommended Group Query,Study 301

Group Query Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)	Brensocatib 10 mg vs. Placebo Risk Difference % (95% CI)	Brensocatib 25 mg vs. Placebo Risk Difference % (95% CI)
Dry skin (GQ)	17 (2.9)	25 (4.4)	8 (1.4)	1.5 (−0.2, 3.4)	2.9 (1.0, 5.1)*
Skin exfoliation	5 (0.9)	7 (1.2)	0	0.9 (0.2, 2.0) *	1.2 (0.5, 2.5)*
Alopecia (GQ)	8 (1.5)	9 (1.6)	2 (0.4)	1.0 (−0.1, 2.4)	1.2 (0.1, 2.6)*
Hyperkeratosis (GQ)	8 (1.4)	16 (2.8)	5 (0.9)	0.5 (−0.9, 1.9)	1.9 (0.4, 3.7)*
Hyperkeratosis	5 (0.9)	15 (2.6)	3 (0.5)	0.3 (−0.8, 1.5)	2.1 (0.7, 3.8)*
Rash (GQ)	25 (4.3)	35 (6.1)	22 (3.9)	0.4 (−2.0, 2.8)	2.2 (−0.4, 4.8)
Rash	16 (2.7)	26 (4.5)	13 (2.3)	0.4 (−1.5, 2.4)	2.2 (0.1, 4.5)*
Hypersensitivity (GQ)	10 (1.7)	15 (2.6)	10 (1.8)	-0.1 (−1.7, 1.6)	0.8 (−0.9, 2.7)
Urticaria	1 (0.2)	10 (1.7)	2 (0.4)	-0.2 (−1.1, 0.6)	1.4 (0.2, 2.9)*

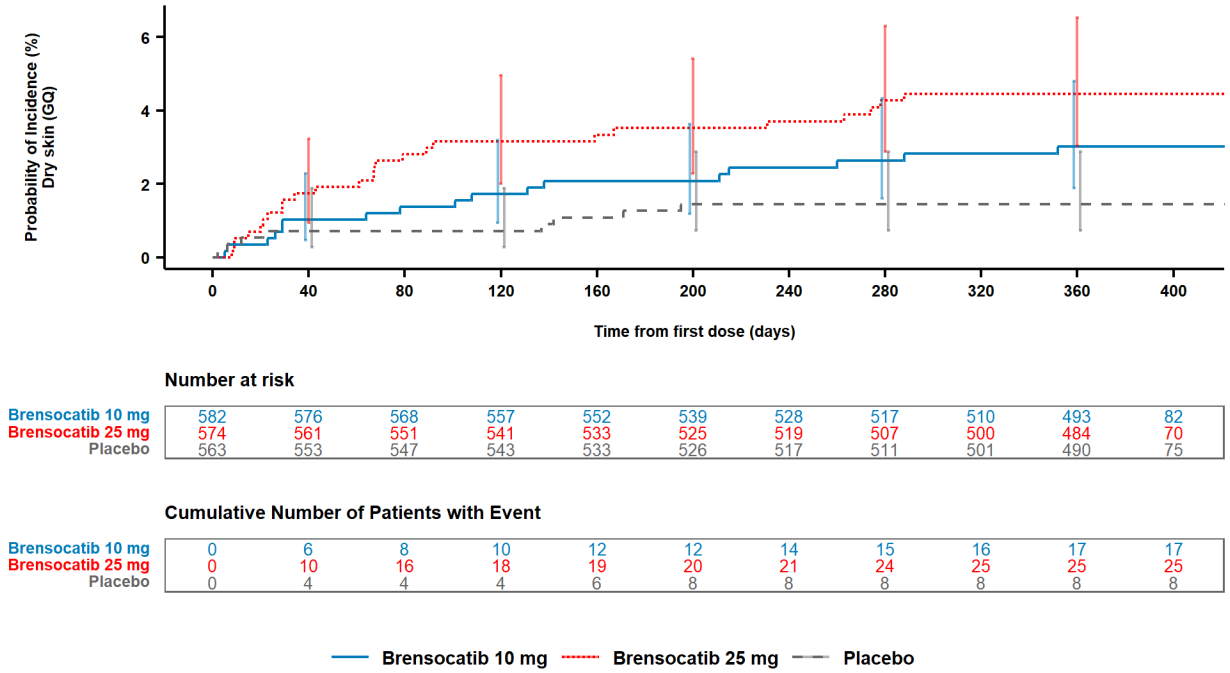
Source: adae.xpt; Software: R
Asterisk (*) indicates that 95% confidence interval excludes the null.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

The GQs of dry skin, alopecia, and hyperkeratosis demonstrated increased incidence in the brensocatib groups but only the brensocatib 25-mg group had a risk difference CI that excluded the null. Similar patterns were observed for the PTs of rash and urticaria but not for the GQ under which they were grouped. Dry skin, alopecia, and hyperkeratosis GQs and urticaria are discussed individually below. Rash is not discussed further as the analysis does not reveal new or different information beyond what is discussed in Section 7.6.1.

Dry Skin-Study 301

The PT of dry skin demonstrated a clear dose-dependent increase in the brensocatib groups compared to placebo, met the Applicant defined threshold of ≥2% in any treatment arm over placebo, and has been incorporated into the adverse reactions table in the Applicant proposed label. In the review of the reported TEAEs for Study 301, risk difference CI for both brensocatib treatment groups included the null (Table 29). However, by GQ analysis, only the brensocatib 25-mg group risk difference CI excluded the null (Table 42). Among the PTs grouped under the GQ of dry skin, skin exfoliation was the only one to demonstrate a risk difference that excludes the null. Interestingly, it is the only PT across all GQs to exhibit this for both dose levels. Dry skin events in Study 301 were mild to moderate in intensity and did not lead to treatment discontinuations. The time to onset depicted in Figure 17 appears similar between the brensocatib groups within the first 6 weeks after which the 25-mg arm demonstrates a more rapid increase in events. Although there remains significant overlap in the CI, the 25-mg group demonstrates a clear separation from the placebo group at Week 40.

Figure 17. Time to Onset of Dry Skin GQ, Safety Population, Trial 301



Number at risk

Brensocatib 10 mg	582	576	568	557	552	539	528	517	510	493	82
Brensocatib 25 mg	574	561	551	541	533	525	519	507	500	484	70
Placebo	563	553	547	543	533	526	517	511	501	490	75

Cumulative Number of Patients with Event

Brensocatib 10 mg	0	6	8	10	12	12	14	15	16	17	17
Brensocatib 25 mg	0	10	16	18	19	20	21	24	25	25	25
Placebo	0	4	4	4	6	8	8	8	8	8	8

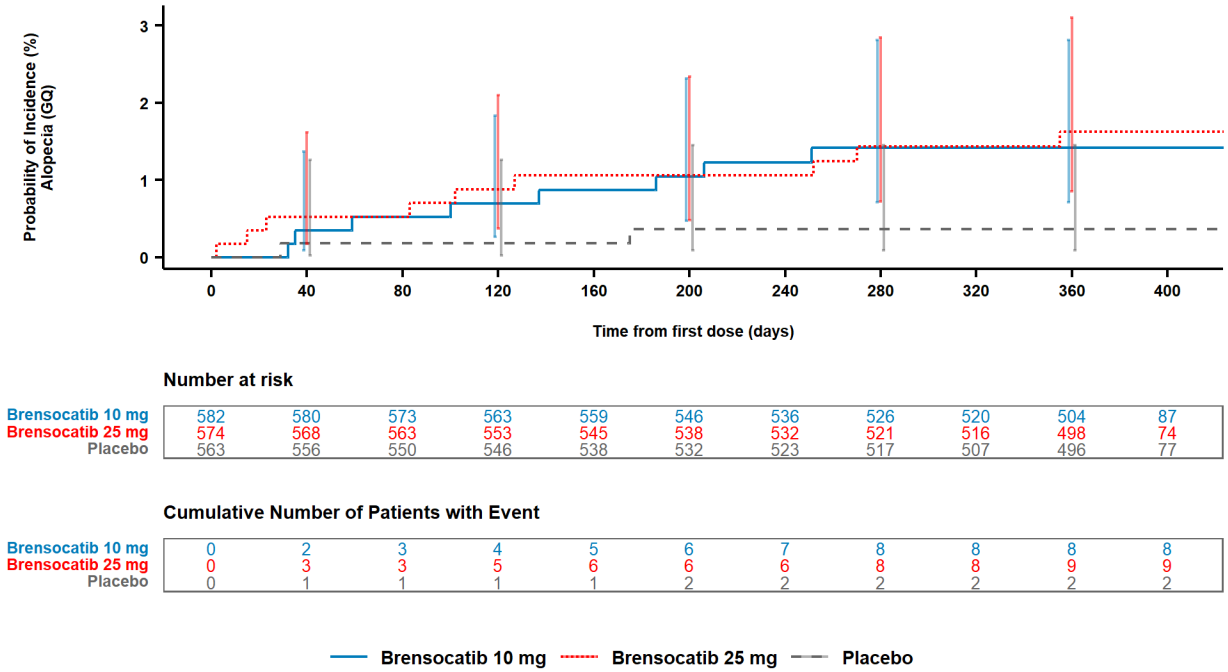
Brensocatib 10 mg Brensocatib 25 mg Placebo

Source: adsl.xpt and adae.xpt; Software: R
Treatment-emergent adverse events defined as preexisting AEs that worsen in severity after the first administration of study drug or AEs that have onset on or after the first administration of study drug through 28 days after the last administration of study drug. Duration is 52 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviations: AE, adverse event; GQ, grouped query

Alopecia-Study 301

Of the 19 alopecia events (1.1% of the total population) in Study 301, 90% occurred in the brensocatib groups with the 25-mg group demonstrating an increased risk difference with a CI excluding the null (Table 42). Alopecia events were predominantly mild with a few moderate events resulting in 2 treatment discontinuations, 1 in each brensocatib group. Time to onset (Figure 18**)** occurred earlier in the brensocatib 25-mg group within the first 40 days compared to the 10-mg group**;** however, there was no substantial difference between groups for the remainder of the treatment period.

Figure 18. Time to Onset of Alopecia GQ, Safety Population, Trial 301



Source: adsl.xpt and adae.xpt; Software: R
Treatment-emergent adverse events defined as preexisting AEs that worsen in severity after the first administration of study drug or AEs that have onset on or after the first administration of study drug through 28 days after the last administration of study drug.
Duration is 52 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviations: AE, adverse event; GQ, grouped query

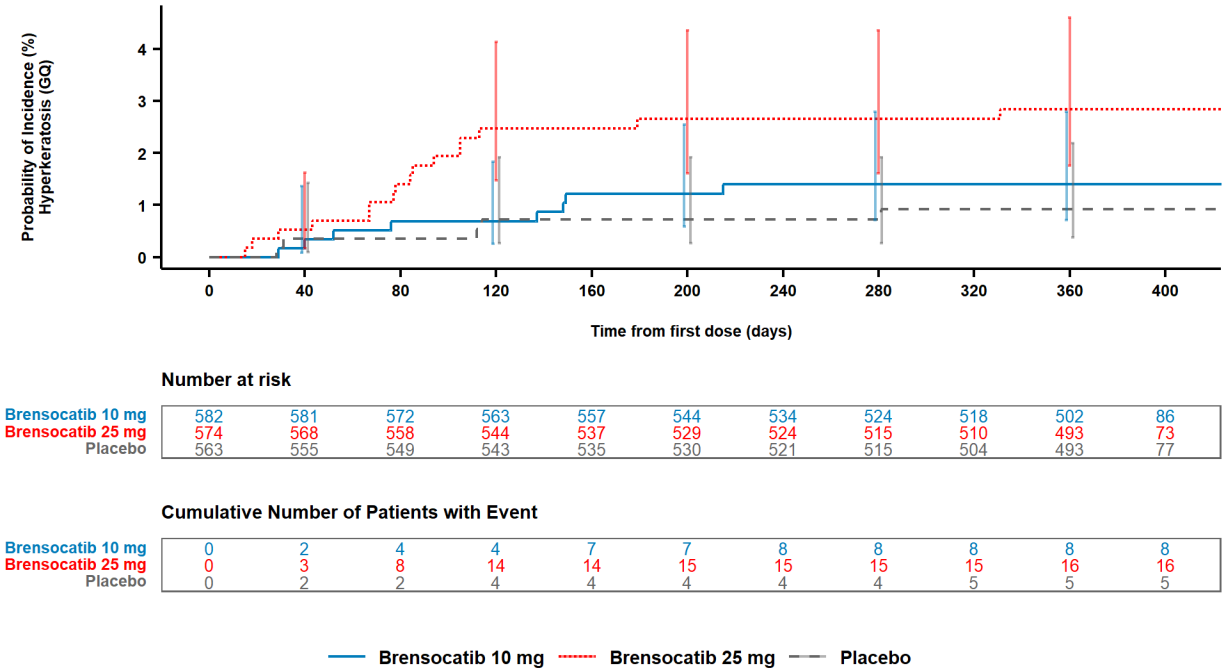
The clinical phenotype of PLS has been reported to include hypertrichosis rather than alopecia. Therefore, the clinically meaning of this observation of treatment-related alopecia with brensocatib is unclear.

Hyperkeratosis-Study 301

Using DDD's recommended groupings for hyperkeratosis, there is a numerical difference in the number of events reported for brensocatib 25 mg and placebo compared to events recorded under the Applicant-defined AESI grouping in Study 301. Specifically, analysis by GQ results in a decrease of 2 events in brensocatib 25-mg group and increase of 1 event in the placebo group (Table 31 and Table 42). Consequently, there is a reduction of the risk difference for brensocatib 25 mg from 2.3 to 1.7; however, the CI still excludes the null.

The difference in number of events with the hyperkeratosis GQ results in differences in the time-to-event analysis (Figure 19) compared to the Applicant's AESI group (Figure 15). In the GQ analysis, there is overlap of the CI between brensocatib 25 mg and placebo across all treatment time points.

Figure 19. Time to Onset of Hyperkeratosis GQ, Safety Population, Study 301



Source: adsl.xpt and adae.xpt; Software: R
Treatment-emergent adverse events defined as preexisting AEs that worsen in severity after the first administration of study drug or AEs that have onset on or after the first administration of study drug through 28 days after the last administration of study drug. Duration is 52 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviations: AE, adverse event; GQ, grouped query

Although there are some numerical differences in the analyses by Applicant-defined AESI grouping compared to DDD's recommended groupings, the overall results continue to demonstrate a dose-dependent increase in hyperkeratosis events with an increased risk difference CI excluding the null in the brensocatib 25 mg.

Hypersensitivity and Urticaria-Study 301

In the analysis of hypersensitivity by GQ, there were a total of 35 events with 15 occurring in the brensocatib 25-mg group and 10 events in both the brensocatib 10 mg and placebo groups, (Table 42). The most common TEAE in the hypersensitivity GQ was urticaria (13 events) with the majority of events occurring in the brensocatib 25-mg group (10 events) where the increased risk difference has a confidence interval excluding zero. One and two events of urticaria occurred in the in the brensocatib 10 mg and placebo groups, respectively. Urticaria events were mild in the brensocatib 10 mg and placebo groups and in 7 out of the 10 events in the brensocatib 25-mg group. Of the remaining 3 events in the brensocatib 25-mg group, 2 were of moderate intensity and 1 was severe. An additional case of mild urticaria was reported in the 120-day safety updating involving a 13-year-old in the 25-mg group (Section 17).

No urticaria events across treatment groups led to treatment discontinuation. Given the small number of events, a time-to-event analysis was not conducted. Overall, urticaria events were rare (0.8% total population), and the clustering of these events in the brensocatib 25-mg group is of unclear clinical significance.

GQ Analysis Results-Study 201

Review of GQ analyses for Study 201 generally appears consistent with the findings of Study 301 with the notable difference of far fewer alopecia (1 subject on placebo) and urticaria (1 subject on brensocatib 25 mg and 1 subject on placebo) events. Given that both occurred at low frequencies within Study 301, it is plausible that the smaller population size of Study 201 was insufficient to detect a meaningful difference.

Summary of Hyperkeratosis and Skin-related Events

In summary, review of the safety databases for Studies 301 and 201 for non-neoplasm skin-related events by recommended DDD groupings supports the finding of the dose-dependent increases in the adverse reactions of hyperkeratosis, dry skin, and rash while also revealing potential rarer adverse reactions of alopecia and urticaria associated with brensocatib 25-mg treatment. The small number of predominately mild urticaria events are of unclear clinical significance.

Neoplasms

As described in Section 7.7.1, a treatment-related increase in skin-related neoplasms was observed in Study 301. As with other skin-related events, DDD provided recommended groupings for the assessment of neoplasms, which are summarized in Table 43.

Table 43. Summary of Neoplasms by Recommended Group Query, Study 301

Group Query Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Benign neoplasm (GQ)	13 (2.2)	13 (2.3)	12 (2.1)
Cyst	1 (0.2)	1 (0.2)	0
Dermal cyst	1 (0.2)	1 (0.2)	0
Eyelid cyst	1 (0.2)	0	0
Lichenoid keratosis	1 (0.2)	0	0
Papule	2 (0.3)	0	1 (0.2)
Seborrheic keratosis	2 (0.3)	3 (0.5)	1 (0.2)
Skin papilloma	2 (0.3)	1 (0.2)	1 (0.2)
Benign neoplasm	0	1 (0.2)	0
Hemangioma	0	1 (0.2)	0
Lentigo	0	1 (0.2)	0
Benign neoplasm of skin	0	0	1 (0.2)
Fibrous histiocytoma	0	0	1 (0.2)
Skin mass	0	1 (0.2)	1 (0.2)
Sweat gland tumor	0	0	1 (0.2)
Skin lesion	3 (0.5)	6 (1.0)	5 (0.9)

Group Query Preferred Term	Brensocatib 10 mg N=582 n(%)	Brensocatib 25 mg N=574 n(%)	Placebo N=563 n(%)
Skin cancer (GQ)	5 (0.9)	11 (1.9)	6 (1.1)
Anal squamous cell carcinoma	1 (0.2)	0	0
Malignant melanoma in situ	1 (0.2)	0	0
Skin cancer	1 (0.2)	0	0
Malignant melanoma	0	2 (0.3)	0
Squamous cell carcinoma	0	1 (0.2)	0
Bowen's disease	0	1 (0.2)	2 (0.4)
Basal cell carcinoma	1 (0.2)	4 (0.7)	3 (0.5)
Squamous cell carcinoma of skin	1 (0.2)	3 (0.5)	3 (0.5)

Source: adae.xpt; Software: R
Duration is 52 weeks.
Abbreviations: GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

The incidence of benign neoplasms was low and comparable across all treatment groups in Study 301. Among skin cancers, the incidence was comparable between brensocatib 10 mg and placebo groups, while there was a slightly greater incidence observed in the brensocatib 25-mg group. In Study 201, there was 1 subject with skin cancers (both basal cell and squamous cell carcinomas) and 11 subjects with benign neoplasms with generally comparable distribution of incidence across treatment groups.

In their review of the data, DDD states that many of these skin cancers are typically due to extensive sun exposure, particularly among adults. Therefore, the 0.8% increase from placebo in the brensocatib 25-mg group is notable but the association with brensocatib is unclear, although plausible based on the mechanism of action.

Conclusion

In conclusion, a detailed review of the observed skin-related disorders in Studies 301 and 201 conducted in accordance with expert guidance by DDD confirmed the primary review team's assessment of dry skin, rash, and hyperkeratosis as important safety signals. These adverse events occur at a high enough frequency to be captured in the adverse reactions table in Section 6 of the USPI. These events were generally mild and rarely resulted in treatment discontinuation; however, as noted in Section 7.6.1.6, referral to dermatologist for treatment was indicated for most subjects who developed new skin findings. In addition, this review identified alopecia, skin cancers, and urticaria as rare adverse events occurring on the 25-mg dose that do not reach the threshold for inclusion in the adverse reactions table. Given the biological plausibility of drug association based on mechanism of action, the dose-dependent distribution, and the actionable guidance to communicate to prescribers (i.e., referral to dermatology), Dermatologic Adverse Reactions, listing rash, dry skin, and hyperkeratosis will be included as a Warning and Precaution in Section 5 of the USPI. Urticaria will not be included because of an overall low incidence and less persuasive biological plausibility of drug-relatedness. Refer to Section 23.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Based on population PK analysis, brensocatib pharmacokinetics is similar in healthy subjects and in patients with NFCB. No dosage adjustment is recommended based on organ (renal or hepatic) impairment, body weight (median [range] =69.7 [31.7, 155] kg), age (median [range] =59 [12, 85] years), race (72% White, 6% Black, and 12% Asian), or gender.

Renal Impairment

No dosage adjustments are recommended for patients with mild, moderate, or severe renal impairment.

A dedicated renal impairment study, INS1007-102, was conducted to evaluate the pharmacokinetics of brensocatib following a single oral administration of 25 mg brensocatib in subjects with mild, moderate, and severe renal impairment, relative to subjects with normal renal function. For additional details, refer to Section 14.2.7. Brensocatib exposure (maximum plasma concentration [C_{max}] and AUC) was comparable in subjects with mild renal impairment (estimated glomerular filtration rate [eGFR]: 60 to 89 mL/min/1.73m^2) compared to subjects with normal renal function (eGFR: ≥90 mL/min/1.73m^2). Brensocatib C_{max} and AUC increased by 10% and 27%, respectively, in subjects with moderate renal impairment (eGFR: 30 to 59 mL/min/1.73m^2), but decreased by 17% and 28%, respectively, in subjects with severe renal impairment (eGFR: 15 to 29 mL/min/1.73m^2) compared to subjects with normal renal function. The observed changes in exposure are not considered clinically relevant. Therefore, no dosage adjustments are recommended for patients with mild, moderate, or severe renal impairment.

Hepatic Impairment

No dosage adjustments are recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, or C).

A dedicated hepatic impairment study, INS1007-105, was conducted to evaluate the pharmacokinetics of brensocatib following a single oral administration of 25 mg brensocatib in subjects with mild, moderate, and severe hepatic impairment, relative to subjects with normal hepatic function. For additional details, refer to Section 14.2.10. Compared to subjects with normal hepatic function, brensocatib C_{max} and AUC increased by 12% and 20%, respectively, in subjects with mild hepatic impairment (Child-Pugh 5 to 6), remained comparable in subjects with moderate hepatic impairment (Child Pugh 7 to 9), and decreased by 26% and 20%, respectively, in subjects with severe hepatic impairment (Child-Pugh 10 to 15). The observed changes in exposure are not considered clinically relevant. Therefore, no dosage adjustments are recommended for patients with mild, moderate, or severe hepatic impairment.

Adolescents

Plasma samples for PK assessment were collected in all adolescents enrolled in Study 301. The observed plasma exposure of brensocatib in adolescents is generally within the same range as the exposure in adults. In population PK analysis, no clinically significant impact of body weight or

age was identified. Refer to Section 6.3.2 for more detailed discussion on the efficacy, safety, and pharmacokinetics of brensocatib in adolescents.

8.2. Extrinsic Factors

Brensocatib may be administered without regard to food. In addition, no dosage adjustments are recommended due to drug-drug interactions.

Food Effect

The effect of food on the pharmacokinetics of brensocatib was assessed in Study INS1007-101. Following a single oral dose of 40 mg, brensocatib exposure (C_{max} and AUC) was comparable under fasted or fed (high-fat and high-calorie) conditions. In the fed state, the median brensocatib time to maximum concentration (T_{max}) was delayed by about 0.7 hours. For additional details, refer to Section 14.2.6. Food was not found to have a clinically relevant impact on the pharmacokinetics of brensocatib. Therefore, brensocatib may be administered with or without food.

Effect of Other Drugs on Brensocatib

Based on data from in vitro studies, brensocatib is mainly metabolized by cytochrome P450 (CYP)3A4. Brensocatib is also a substrate of the transporters P-gp and BCRP.

The Applicant conducted three clinical drug-drug interaction (DDI) studies to explore the impact of other drugs on brensocatib PK. Study D6190C00003 evaluated the impact of a moderate CYP3A4 and P-gp inhibitor (verapamil) and a strong CYP3A4 inhibitor and P-gp inhibitor (itraconazole). Study INS1007-109 evaluated the impact of a strong CYP3A4 and P-gp inhibitor (clarithromycin). Study INS1007-106 evaluated the impact of a strong CYP3A4 inducer (rifampin), and an acid reducing agent (esomeprazole). Notably, in Study D6190C00003, co-administration of brensocatib with itraconazole yielded a 39% decrease in brensocatib C_{max} and a 14% increase in brensocatib AUC. A decrease in C_{max} is not the expected consequence of CYP3A4 inhibition. The observed effects on brensocatib following co-administration with itraconazole may have been because the solution formulation of itraconazole used (i.e., Sporanox) contains the excipient hydroxypropyl-β-cyclodextrin (HP-β-CD), which may impact the rate and extent of victim drug absorption due to formation of a pre-systemic complex between excipient and drug. Therefore, the change in brensocatib exposure following co-administration with itraconazole is not representative of the impact of a strong CYP3A4 inhibitor. The Applicant therefore conducted Study INS1007-109 using clarithromycin as an index inhibitor to evaluate the effect of strong CYP3A4 inhibition on the pharmacokinetics of brensocatib. For additional details, refer to Sections 14.2.5, 14.2.8, and 14.2.9.

When co-administered with the strong CYP3A4 and P-gp inhibitor, clarithromycin, brensocatib C_{max} and AUC increased by 68% and 55%, respectively, relative to that after administration of brensocatib alone. Meanwhile, when co-administered with the moderate CYP3A4 and P-gp inhibitor, verapamil, brensocatib C_{max} and AUC increased by 53% and 32%, respectively, relative to that after administration of brensocatib alone. When co-administered with the strong CYP3A4 inducer rifampin, brensocatib C_{max} and AUC decreased by 15% and 33%, respectively, relative to that after administration of brensocatib alone. When co-

administered with the proton-pump inhibitor esomeprazole, brensocatib C_{max} and AUC were unchanged compared to that after administration of brensocatib alone.

As expected, a smaller magnitude of effect on brensocatib AUC was observed following co-administration with verapamil (moderate CYP3A4 inhibitor) relative to clarithromycin (strong CYP3A4 inhibitor). However, a similar magnitude of effect on brensocatib C_{max} was observed, which may be because both verapamil and clarithromycin are inhibitors of P-gp. The data suggest that P-gp plays a key role in brensocatib absorption following oral administration. In exposure-response analyses for safety, no relationship was observed between brensocatib systemic exposure (steady-state AUC_{τ}) and adverse events of periodontal disease or pneumonia. While an AUC-dependent trend for mild and moderate hyperkeratosis was detected, the predicted probability of hyperkeratosis (summarized as geometric mean) was considered low at both 10 mg (1.55% in adults, 1.73% adolescents) and 25 mg (3.01% in adults, 3.36% in adolescents) as compared to placebo (0.52% in adults and adolescents). In addition, there are currently no approved therapies for the treatment of NCFB. As doses of 10 mg and 25 mg are proposed to-be-marketed for the treatment of NCFB, doses may be adjusted for tolerability as clinically indicated. Therefore, the increase in brensocatib exposure by up to 55% due to DDIs is not considered clinically relevant. Also refer to Section 7 for additional details on the safety assessment and Section 14.5 for additional details on exposure-response analysis.

Overall, no dosage adjustments are recommended when brensocatib is co-administered with CYP3A4 inhibitors, CYP3A4 inducers, P-gp inhibitors, or acid-reducing agents.

No clinical DDI studies were conducted to evaluate the impact of BCRP inhibitors alone on brensocatib exposure. However, based on data from mass balance Study INS1007-103, the estimated oral bioavailability of brensocatib was approximately 80% or higher (determined based on the total dose recovered in urine and feces and the amount of unchanged brensocatib detected in feces). As a high proportion of brensocatib is absorbed following oral administration, it is unlikely that co-administration of brensocatib with BCRP inhibitors will result in large increases in brensocatib exposure. Therefore, BCRP inhibitors are unlikely to have a clinically relevant impact on brensocatib pharmacokinetics.

Effect of Brensocatib on Other Drugs

Based on in vitro studies, brensocatib was identified as a potential weak CYP3A4 inducer. The Applicant conducted PBPK analysis to predict the impact of brensocatib on the sensitive CYP3A4 substrate, midazolam. Based on PBPK analysis, co-administration of brensocatib is unlikely to have a clinically significant impact on CYP3A4 substrate exposure. For additional details on PBPK analysis, refer to Section 14.5

In vitro studies indicated that at clinically relevant concentrations, brensocatib is not likely to inhibit or induce other common CYP enzymes. In addition, at clinically relevant concentrations, brensocatib is not likely to inhibit other transporters. For additional details, refer to Section 14.1.

8.3. Plans for Pediatric Drug Development

As a new molecular entity for a new indication, this application for brensocatib is subject to the requirements of the Pediatric Research Equity Act (PREA). In accordance with the PREA, the Applicant submitted an initial pediatric study plan (iPSP) for brensocatib for the treatment of

NCFB on September 3, 2020. The Applicant initially requested a full waiver of pediatric assessments citing feasibility concerns given the lower prevalence of NCFB among pediatric patients. In a written response to the iPSP, dated November 3, 2020, the Agency stated that although the prevalence of disease is low among pediatric patients, adolescents should be included in the phase 3 program because the epidemiology of NCFB is actively evolving to indicate higher incidence, there are no approved therapies for NCFB, and there is sufficient overlap in the underlying etiologies and shared pathophysiology of disease between adults and adolescents. Prospect of direct benefit to justify enrollment of adolescents in Study 301, in accordance with 21 CFR Part 50 Subpart D,[1] was demonstrated by Study 201 results. The agreed iPSP, dated on March 26, 2021, included the Applicant's plan to enroll adolescents in the phase 3 program, defer studies in patients aged 6 to <12 years of age, and a waiver of studies in children <6 years of age. A waiver was granted in children <6 years of age given the infeasibility of conducting studies in this population who have too low an incidence of NCFB.

On October 26, 2021, the Applicant submitted an amended iPSP incorporating the agreement with the European Medicines Agency Pediatric Committee for an open-label safety and pharmacokinetic study in 20 subjects aged 6 to <12 years as well as other European Medicines Agency Pediatric Committee approved studies for developing a weight-based, oral liquid dosage form in this population. In addition, the amendment removed the Applicant's planned nonclinical (b) (4) study and, instead, leveraged weight-of-evidence from the available safety data, which do not suggest a greater risk for patients of 6 to <12 years of age than those of ≥12 years of age. The Agency agreed with the Applicant's position in the Amended Agreed iPSP dated May 16, 2022. Further nonclinical studies may be warranted if additional safety signals arise for lower age group populations.

On May 26, 2022, an inadequate proposed pediatric study request (PPSR) notification was issued to the Applicant for the proposed pediatric study in subjects aged 6 to <12 years. The Agency agreed with the plan to develop an age-appropriate dosage form as well as the plan to evaluate brensocatib in this population. However, as stated in Agency comments in the Amended Agreed iPSP, the Agency reiterated that it was premature to reach agreement on a proposed pediatric study request given that the design, safety monitoring, and endpoints of a study in children aged 6 to <12 years would need to be informed by the results of Study 301.

Following approval, the indication for brensocatib will include patients with NCFB ages 12 years and older. This is based on the efficacy and safety data obtained from the phase 3 trial (Study 301) which enrolled 41 subjects aged 12 to <18 years (reviewed in Sections 6.3.2), and also by relying partially on the extrapolation of the efficacy and safety data in adults A PMR will be issued with this approval for a pediatric study in children ages 6 to <12 years and is discussed in Section 24.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 13.

[1] See https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/subpart-D

Table 44. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	• In pregnant rats orally administered brensocatib up to 100 mg/kg/day from 2 weeks prior to mating through organogenesis, no maternal toxicities were observed (128 times the MRHD). Drug-related adverse skeletal malformation of bent scapula was observed in the fetuses of female rats administered 100 mg/kg/day (128 times the MRHD on an AUC basis at a maternal oral dose of 100 mg/kg/day). • In pregnant rabbits administered brensocatib at oral doses of 0, 5, 15, and 50 mg/kg/day, decreases in body weight gain were observed in the pregnant rabbit at 15 and 50 mg/kg/day (5 and 20 times the MRHD, respectively). No developmental toxicities were observed in the fetus up to 50 mg/kg/day (20 times the MRHD on an AUC basis at a maternal oral dose of 50 mg/kg/day). • In a pre- and postnatal development study in pregnant rats, no drug-related maternal toxicity or effect on reproductive parameters was noted at oral maternal doses up to 20 mg/kg/day (17 times MRHD).
8.2 Lactation	• Brensocatib was detected in the plasma of rat pups when pregnant rats were administered up to 20 mg/kg/day brensocatib from Gestation Day 6 through Lactation Day 20. While this suggests exposure to brensocatib via maternal milk during lactation, in the absence of measurements directly from maternal milk, this information will not be included in the label.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	• In male rats, daily oral administration of brensocatib for 10 weeks prior to mating did not affect fertility or mating performance at oral doses up to 50 mg/kg/day ((b) (4) times MRHD on an AUC basis). • In female rats, once daily administration of brensocatib did not affect female estrous cycle, mating, mean pre-coital intervals, fertility index, or implantation at oral doses up to 100 mg/kg/day ((b) (4) times MRHD on an AUC basis).

Source: Reviewer generated table
Abbreviation: AUC, area under the concentration-time curve; MRHD, maximum recommended human dose

Table 45. Brensocatib Exposure Margins in Reproductive and Development Toxicity Studies

Study		NOAEL (mg/kg/day)	AUC (µmol.h/L)	Systemic Exposure Margin[a]
Fertility	Male rat[b]	50	1460	154
	Female rat[c]	100	1240	128
EFD rat	Maternal[c]	100	1240	128
	Development[d]	20	403	42
EFD rabbit[e]	Maternal	5	15.1	1.6
	Development	50	195	21
PPND rat[f]		20	163	17

Source: FDA Pharmacology Toxicology Reviewer table
[a] Clinical exposure in Study INS1007-201 was 4173 ng.h/mL or 9.5 µmol.h/L for 25 mg QD dosing of brensocatib
[b] AUC_{0-24} for male fertility is obtained from fertility studies incorporated into the 26-week repeat dose toxicity study (Study #528313)
[c] AUC_{0-24} for female rats was obtained from dose range finding study in pregnant rats (Study #497631)
[d] AUC_{0-24} from Study #497825
[e] AUC_{0-24} for rabbits was obtained from Study# 497626
[f] AUC_{0-24} from PPND study in rats (Study# 00335001).
Abbreviations: AUC, area under the concentration-time curve; EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 217673 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

CMC Summary for IAMA Review

Drug Substance

The drug substance, brensocatib, is manufactured (b) (4) (b) (4) (b) (4) that are consistent with the recommendations of the International Council for Harmonisation (ICH) scientific guideline *Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* (February 2013b). Synthetic schemes as well as the specifications, test procedures, and analyses data for the starting materials are provided and are adequate. In addition, sufficient information for the drug substance synthesis is also provided, which include the synthetic scheme, narrative descriptions, critical process parameters, in-process controls, and specifications for the (b) (4) as well as information about the development of the synthesis.

The drug substance structure is characterized with typical spectrometric techniques. In addition, single-crystal x-ray diffraction results also support the structure and absolute configuration of the two chiral centers of the drug substance.

The NDA includes adequate information for potential and observed impurities in the drug substance. (b) (4) (b) (4) the Applicant has confirmed that the levels of (b) (4) the drug substance are well below the acceptable intake (AI) amount confirmed by the nonclinical team. In addition, the Applicant has demonstrated that mutagenic and other (b) (4) impurities are (b) (4) (b) (4) to levels that are considered to be safe. The elemental impurity (b) (4) is included in the drug substance specification with a limit that is within the recommendations of ICH harmonised guideline *Q3D(R2) Guideline for Elemental Impurities* (April 2022). The drug substance specification is also consistent with the recommendations outlined in ICH harmonised tripartite guideline *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (October 1999), ICH scientific guideline *Q3C(R9) Guideline on Impurities: Guideline for Residual Solvents* (April 2024), and ICH harmonized guideline *Q3D(R2) Guideline for Elemental Impurities* (April 2022). The acceptance criteria limits that are above the ICH guidance for industry *Q3A Impurities in New Drug Substances* (June 2008) qualification threshold for various specified ordinary organic impurities, have been found to be acceptable by the nonclinical team.

Sufficient information has been provided in support of the reference standards necessary for analysis of the drug substance.

The drug substance container closure system is typical of those accepted by the Agency for solid drug substances. Stability data provided for the drug substance supports a (b) (4) month retest period for storage between (b) (4) °C.

The NDA is recommended for approval from the drug substance CMC perspective.

Drug Product

The proposed maximum daily dose of Brinsupri (brensocatib) tablet drug product is 25 mg once daily and there are two strengths: 25 mg and 10 mg. The tablet core and the (b) (4) film coating are manufactured with United States Pharmacopeia (USP)/NF grade excipients in amounts below maximum levels for approved oral drug products, as per the Inactive Ingredient Report.

(b) (4)

The drug product specification includes all parameters that are recommended for a tablet drug product in ICH harmonised tripartite guideline *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (October 1999) and the tablets have a debossed code imprint as required by 21 CFR 206.10. Method validation reports support the analytical methods for identity, assay, drug degradants, and the chromatographic part of the dissolution methods and they all are considered to be suitable for regulatory purposes.

As the drug product is an oral film-coated tablet, the degree of concern regarding the packaging and the likelihood of dosage form-packaging interaction are low. The primary container closure system is a (b) (4) high-density polyethylene bottle with (b) (4) cap.

The Applicant has identified two drug product impurities, (b) (4) and has indicated the mechanism of formation. As noted above, the drug substance contains a (b) (4) were high (out-of-specification or OOS) for the registration stability batches, with some batches showing levels that would result in daily exposures of greater than (b) (4) ng. The non-clinical team agrees with the Applicant's proposed AI of not more than (b) (4) ng/day ((b) (4) ppm in the drug substance for the 25 and 10 mg strengths, respectively) for (b) (4) based on enhanced Ames testing results (see Section 13.2.1). The elemental impurities test results for the three registration batches revealed that Class (b) (4) elemental impurities were below (b) (4)% of the oral permitted daily exposure for all three baches of each strength. Thus, as per the recommendations of ICH harmonized guideline *Q3D(R2) Guideline for Elemental Impurities* (April 2022), no additional controls are necessary.

Because of the levels of (b) (4) in the registration stability batches, the Applicant subsequently manufactured additional supportive drug product batches using (b) (4) (b) (4) and placed samples from these into the stability program.

The Application provided up to 18 months of long-term (25°C/60% RH) stability data for three registration batches of each strength and 6 months of accelerated (40°C/75% RH) stability data

for all registration batches of both strengths. With regard to the (b) (4) impurity, the Applicant submitted up to 6 months of long-term and accelerated stability data for multiple supportive batches of the 25 mg and 10 mg strength product manufactured with (b) (4) (b) (4) Based on the totality of the data and the fact that the Applicant has committed to monitor and discuss any out-of-specification results with the Agency, it is reasonable to grant the 24-month shelf life proposed in the interim, as more data are being collected.

Manufacturing/Facilities

The manufacturing process for both strengths of Brinsupri (brensocatib) tablet drug product includes (b) (4)
The registration batches and the proposed commercial batches have the same manufacturing process.

Batch size comparison between the registration batch and commercial batch:

The registration batches for both strengths, e.g., bulk batch CMXTP (25 mg strength in seq#0001) and batch CMNYC (10 mg strength, added in seq#0017), are the same, i.e., (b) (4) tablets per batch or about (b) (4) kg per batch, and the proposed commercial batch size is (b) (4) per batch or about (b) (4) kg per batch. The scale up is (b) (4) fold from registration stability to commercial batches.

Scale up commercial size batches:

To support the scale up, the Applicant manufactured scale-up commercial size batches ((b) (4) kg) by using the intended commercial manufacturing equipment and proposed parameters, including three 10 mg strength batches and two 25 mg strength batches. The 10 mg strength tablets proposed as commercial drug product in seq#0017 have the (b) (4) as the 25 mg strength. Therefore, the drug loading is only ~ (b) (4) % w/w per unit for 10 mg strength, presenting a (b) (4).

The associated data for these 5 commercial size batches are presented in "Manufacturing Process Development" report in 3.2.P.2 and have been evaluated. In summary, the proposed equipment, process parameters and in-process control/test specification ranges are justified by these five commercial size batches.

The drug substance and drug product manufacturing facilities are found acceptable based on inspection history.

Biopharmaceutics

The biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data supporting the dissolution method and acceptance criteria as well as the bridging of formulation changes made during development.

The dissolution method uses USP Apparatus 2 (paddle) with rotation speed of 65 rpm, 500 mL of 0.1 N hydrochloric acid medium at 37°C and an acceptance criterion of Q = (b) (4) % in 30 minutes. The method is found to be adequate for drug release testing of the drug product as per specification.

Brinsupri (brensocatib) tablets are immediate release film-coated tablets with two strengths (10 and 25 mg), and these were used in the phase 2 and phase 3 studies as well as a majority of phase 1 studies. Phase 2 tablets and phase 3 tablets (10 mg, and 25 mg) have the same respective core compositions, (b) (4) were used for each strength. The intended respective commercial formulations of 10 and 25 mg strength tablets are identical for the core tablet formulations, shapes, and sizes used across the clinical development program, however the (b) (4) (b) (4) The drug substance used in the phase 2 tablets was manufactured at (b) (4) For the phase 3 tablets and intended commercial tablet formulations, the drug substance manufacturing site was transferred to Esteve Quimica, SA, Spain (Esteve). During clinical phase 2, the drug product manufacturing site also changed from (b) (4), to Patheon, Ontario, Canada. To bridge the tablets used during development and the commercial drug product, comparative dissolution studies were conducted to compare the dissolution profiles of phase 2, phase 3, and commercial drug product at pHs of 1, 2, 4.5, and 6.8 using the quality control dissolution method conditions. Based on the results, the Applicant adequately bridged the clinical and commercial formulation drug products.

From a biopharmaceutics perspective the application is recommended for approval.

9.1. Device or Combination Product Considerations

This section is not applicable to the review of brensocatib tablets.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Good Clinical Practice Compliance

The Applicant stated that the trial was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and applicable ICH harmonised guideline *E6(R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice* (November 2016). The study protocol and amendments, informed consent form, investigator brochure, and other necessary documents were reviewed and approved by an independent ethics committee (IEC) or an institutional review board as appropriate. Written Informed Consent was obtained prior to study participation.

Data Quality Assurance

To ensure data quality, the Applicant conducted investigator trainings for clinical research associates, and individual site initiation meetings in addition to regular site monitoring and a GCP audit program to assess compliance with GCP procedures.

Investigations for serious GCP noncompliance issues were conducted during the study for which all relevant health authorities and IEC/ institutional review boards were notified as per applicable laws and regulations. These investigations are summarized below:

- Uncertified Subinvestigator: This breach pertained to an uncertified subinvestigator in New Zealand and resulted in site screening activities being placed on hold until corrective actions and preventative measures were implemented at the site by the contract research organization. The Applicant deemed the breach did not impact the scientific validity of the data and lifted the screening hold. No subject data was excluded as a result of the breach.
- Lack of Accountability and Responsiveness to GCP Noncompliance Issues: In accordance with 21 CFR 312.56(b), the Applicant terminated study participation of a US Investigator for lack of accountability and responsiveness to significant GCP noncompliance issues that included but were not limited to inadequate principal investigator oversight and noncompliance with the protocol. The Applicant and the contract research organization were prevented from conducting site monitoring activities as required per protocol and GCP. A total of two subjects were enrolled at the site with one having discontinued and one on study at the time of Investigator termination. The on-study subject was not transferred to another site per the subject's decision. Because the Applicant was unable to verify all study visit data and resolve outstanding queries, data collected from this site were not included in the analysis.
- Deviation From Argentina Ministry of Health (MoH) Requirement for Tuberculosis (TB) Testing at Screening: Following a protocol review by the Argentina MoH, the ICF was updated to include TB testing during screening to confirm eligibility, guidelines for TB testing were issued for study sites in Argentina, and local IECs and Investigators signed a commitment letter indicating their acknowledgement of the TB testing requirement. It was later noted that TB testing was not completed for 28 subjects in screening and 23 subjects randomized across 14 sites in Argentina. New screenings and randomizations were placed on hold until all subjects had been tested (all were negative) and all sites and employees were retrained on the requirements of the commitment letter. The MoH was notified and confirmed the study could continue.

Financial Disclosure

The Applicant provided adequately disclosed potential financial interests and arrangements by clinical investigators as recommended in the FDA guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators* (February 2013a) (See Section 25 for more information). In addition, the Applicant stated that no investigators/sub-investigators participating in either trial were part-time or full-time employees.

11. Advisory Committee Summary

An advisory committee meeting or other external consultations were not required as part of this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

Brensocatib was originally developed by [redacted] was subsequently out licensed to Insmed Incorporated in late 2016. A PIND meeting was scheduled for June 8, 2017, but was subsequently cancelled by the Applicant upon receipt of preliminary comments. IND 133790 was opened August 13, 2017, and received Breakthrough Designation therapy on June 5, 2020. Table 46 summarizes the key regulatory interactions and Agency advice given to the Applicant throughout the clinical development.

Table 46. Summary of Regulatory History Under IND 133790

Date	Regulatory Event	Key Agency Advice Given
07/08/2020	Type B End of Phase 2 meeting	• The Agency discussed the acceptability of a single phase 3 study design, with a supportive phase 2 trial, if the phase 3 study is well-designed and statistically robust. • The Agency recommended NCFB enrollment criteria be as inclusive as possible for greater generalizability and provided explicit recommendations for an adequate clinical pharmacology program to support an NDA.
03/26/2021	Agreed iPSP	• The Agency recommended inclusion of adolescent patients aged 12 to <18 years in the phase 3 trial based on prospect of direct benefit from phase 2 results and agreed with deferral of pediatric study in patients aged 6 to <12 years pending review of phase 3 trial data.
05/26/2022	Inadequate PPSR sent.	• The Applicant submitted a PPSR proposing a phase 2, open-label study enrolling 20 pediatric patients aged 6 to <12 years with NCFB. The Agency stated it was premature to agree on a study in this age group as the study design needed to be informed by the phase 3 pivotal trial data in adults and adolescents.
12/05/2022	Type B Meeting	• Clinical pharmacology guidance issued for requirements of a DDI data package, population-PK modeling, and bioavailability clinical studies to support an NDA.
04/17/2023	Type C Meeting	• CMC agreed to proposed tablet formulation bridging approach.
08/25/2023	Type B Meeting	• The Agency agreed with the Sponsor's proposal not to pool efficacy but to provide a side-by-side format in the Summary of Clinical Efficacy and with the overall strategy for data presentation for pooling of safety and tolerability data from Studies 201 and 301.
12/11/2023	Type D Meeting	• The Agency reviewed the Sponsor-submitted data and agreed with the proposal to forego further nonclinical or clinical testing for abuse liability and immunotoxicity.
01/18/2024	Type B Meeting, pre-NDA Meeting	• The Sponsor requested guidance on the presentation and formatting of the clinical data package for submission, safety data strategy and proposed SAP analysis specifically analyses related to the adolescent subpopulation. – The Agency recommended utilization of a Bayesian approach for adolescent efficacy analyses and upconverting Study 201 safety data to the latest MedDRA version for the integrated safety summary. – The Agency disagreed with the plan to remove multiplicity control from the time to first pulmonary exacerbation (PEx) and annualized rate of severe PEx endpoints. • The Sponsor provided rationale for their proposal to decrease the interval defining separate exacerbation events from 28 to 14 days in Study 301. The Agency found this acceptable so long as the data remained blinded, and exacerbations were captured in a manner to allow an accurate count based on the revised definition.

Source: Clinical Reviewer.
Abbreviations: iPSP, initial pediatric study plan; NDA, new drug application; PPSR, proposed pediatric study request.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

Brensocatib is a reversible and competitive inhibitor of recombinant human DPP1. It inhibits DPP1 in recombinant enzymes as well as U937 cells. The half-maximal inhibitory concentrations (IC_{50}s) for recombinant rat, dog, and human DPP1 were 17nM, 17nM, and 9nM, respectively. Brensocatib dose-dependently inhibits NSPs- NE, PR3, and CatG activities in differentiated human bone marrow derived neutrophils in vitro but not as recombinant enzymes. Degradation of elastin, a key connective tissue component of the lung, was significantly inhibited by lysates from brensocatib-treated CD34+ bone marrow-derived human neutrophil progenitor cells with an IC_{50} value of 1.8μM.

Data from in vivo models shows brensocatib significantly reduced NE, PR3, and CatG activities in various mice and rat species including C57, BALB/c, Db/Db and NZBWF1/J mice, and Sprague Dawley and Wistar Han rats. Mice and rats were administered a range of oral doses of brensocatib between 0.2 mg/kg/day to 100 mg/kg/day either once or twice daily for 7-14 days in various studies. Both twice daily (BID) and QD dosing reduced levels of NSPs. NE was reduced by 16 to 89%, PR3 by 46 to 85% and CatG by 32 to 99%. Both dosing strategies increased the systemic concentrations with increase in dose and reduced NSPs, independent of strain and species. It was also confirmed that NSPs were inhibited to a similar extent in *CFTR* knockout mice therefore indicating that the *CFTR* gene does not affect brensocatib activity. The maximum PD effect was observed at 7 days post-dose in repeat dose studies. A duration-dependent reduction in NSP activities was observed in time to reach 50% reduction in activity, reaching a maximum reduction at 7 days and plateauing subsequently. DPP1 activity increased on Day 1 post-dose but plateaued around Day 7. The NSP activity showed recovery to baseline levels approximately 10 days after stopping dosing.

There are no established models for non-cystic fibrosis bronchiectasis. Therefore, the Applicant has evaluated the activity of brensocatib in an acute lung injury model. In an LPS-induced lung injury model in Sprague Dawley rats, 0.2, 2, or 20 mg/kg brensocatib was orally administered twice daily for 8 days prior to intratracheal LPS challenge. NSP activity in blood, BAL, and bone marrow was variably reduced in the brensocatib-treated groups 24 hours post-LPS challenge. Brensocatib only reduced TNFα levels with no effect on other cytokines or hydroxyproline levels. In an LPS-induced lung injury model in BALB/c mice, 3 or 30 mg/kg brensocatib was administered twice daily for 7 days prior to intranasal LPS challenge. At 2 and 5 days post-LPS challenge, NSP levels were reduced in the bone marrow of brensocatib-treated mice compared to vehicle or dexamethasone-treated mice. However, brensocatib treatment did not affect the other measures of acute lung injury including body and lung weights, cytokine levels, neutrophil levels in BAL fluid, and lowered respiratory capacity in animals.

13.1.2. Safety Pharmacology

Safety pharmacology studies indicated that brensocatib did not affect the central nervous system or respiratory system in Han Wistar rats at oral doses up to 200 mg/kg (>140 times MRHD by AUC or 38 times MRHD on an AUC basis). In a good laboratory practice (GLP) telemetric assessment of cardiovascular activity in Beagle dogs, brensocatib did not induce any changes at oral doses up to 50 mg/kg (>6 times MRHD on an AUC basis or 33 times on a body surface area basis). At oral doses of 1000 mg/kg, increased heart rate, diastolic blood pressure, mean blood pressure, QA interval, and QTcR interval were observed up to 8h post-dose (>862 times MRHD on an AUC basis). In a non-GLP study in guinea pigs, brensocatib did not affect cardiovascular parameters when administered intravenously up to 9.6 mg/kg. In GLP studies, brensocatib inhibited stably expressed hERG channels in Chinese hamster ovary cells with an IC_{50} of 13.9µM.

Absorption, Distribution, Metabolism, Excretion/PK

Brensocatib was administered intravenously at 1 mg/kg in male rats and 2.5 mg/kg in dogs. The elimination half-life ($T_{1/2}$) was 5.2 hours in rats and 18 hours in dogs; the volumes of distribution (Vss) was 2.5 L/kg in rats and 11 L/kg in dogs; and the plasma clearance was 6.5 mL/min.kg in rats and 7.6 mL/min.kg in dogs. For oral administration, rats were administered 2.5 mg/kg, and dogs were administered 2 mg/kg brensocatib. The absorption speed was moderate with T_{max} ranging from 3 to 6 hours. The $T_{1/2}$ was comparable to intravenous route for rats and dogs, respectively. The oral bioavailability was 75% and 92% for rats and dogs, respectively.

Plasma protein binding was moderate (~70.3%) in dog and high (~93.9%) in rat. In human plasma samples, the plasma binding was ~87.3%. In male albino rats, brensocatib was widely distributed with the highest concentrations of radioactivity detected in the liver and preputial gland. In male pigmented rats, the highest concentrations of radioactivity were detected in the uveal tract. Radioactivity was also detected in the whole eye. The consistent radioactivity noted in the uveal tract and tissue surrounding the brain of the pigmented rats was further concluded to be attributable to melanin pigments located within the meninges of the brain, localized around but not in blood vessels. The concentration was higher in pigmented skin versus non-pigmented skin. In pregnant female albino rats, besides similar tissue distribution of radioactivity to male albino rats, radioactivity was also detected in the amniotic sac and placenta, and in fetus liver, fetus, and amniotic fluid suggesting the placental transfer of the radioactivity.

In in vitro metabolism studies, CYP3A4 and CYP3A5 were identified as the major CYP isoforms involved in brensocatib metabolism. The major metabolic pathways of brensocatib were believed to be oxidations on the oxazepane ring, but not N-demethylation. In a covalent binding study of $^{[14C]}$brensocatib to human hepatic proteins, a fraction of 0.0188 of $^{[14C]}$brensocatib was found to covalently bind to human hepatocytes after a 4-hour incubation. Metabolism and excretion of brensocatib was also evaluated in Han Wistar rats and beagle dogs. Thirty total metabolites were detected. The major metabolite detected was thiocyanate which accounts for 67% of dog plasma radioactivity. Feces was the major source of excretion in both species, followed by urine.

13.1.3. General Toxicology

Repeat Dose Toxicology Studies in Rats

4-Week Rat Study (Study #527409)

In a GLP study, Wistar Han rats were administered brensocatib once daily for four weeks at 0 (vehicle), 3, 15, and 100 mg/kg by oral gavage. There were no early mortalities in the study. There were slight elevations in neutrophils and reticulocytes in both sexes and platelets in males. Elevated levels of alkaline phosphatase and phosphate levels were observed in males and increased bile acids were observed in both sexes. Higher ALP was correlated with increased kidney weight and tubular vacuolation and basophilia in high dose (HD) animals. The vacuolation was observed in recovery animals as well. These findings were considered adverse. Additionally, higher lung weight and increased alveolar macrophage aggregation was observed in high dose animals. These findings were not observed in recovery animals. The no observed adverse effect level (NOAEL) was concluded to be 15 mg/kg/day with an $AUC_{0\text{-}24}$ of 270 µmol.h/L and C_{max} of 27.3 µmol/L.

26-Week Rat Study (Study # 528313)

In rats administered 0 (vehicle), 3, 9, or 50 mg/kg/day brensocatib for 26 weeks in a GLP study, drug-related adverse findings were evident in lung and kidney in the 50 mg/kg dosing group. In lung, diffuse vacuolated macrophage accumulation (minimal to marked) and cellular debris (mild) were noted. PLD was confirmed upon TEM examination with lamellar lipid structures observed in these vacuoles. It is believed that drug induced PLD is associated with the physiochemical property of the compound as cationic amphiphilic. In kidney, minimal to mild tubular basophilia in the outer medulla was noted, which correlated to the increase of NAG and NAG/creatinine ratio, an early sensitive indicator of acute renal tubular injury. Seminal vesicle gland weight was decreased by ~20%. However, there were no histopathological correlates and the drug at up to 50 mg/kg/day did not affect male mating performance and fertility. All the above changes were reversible. The NOAEL was 9 mg/kg/day for general toxicity, which corresponded to an $AUC_{0\text{-}24h}$ of 196µmol·h/L and C_{max} of 17.8µmol/L on Day 182.

Repeat Dose Toxicology Studies in Beagle Dogs

4-Week Dog Study (Study #527414)

In a GLP study, beagle dogs were administered brensocatib once daily for four weeks at 0 (vehicle), 3, 15, and 75 mg/kg by oral gavage. There were no early mortalities, but excessive salivation and mucousy vomit, attributed to regurgitated test article, was observed in the 75 mg/kg/day treated animals. Changes in electrocardiogram (ECG) parameters including increased heart rate and decreased PR and Qt intervals were observed immediately post-dose in the 75 mg/kg/day group. Increases in AST, ALT, glutamate dehydrogenase, and myoglobin were observed in a dose dependent manner which resolved in the recovery period, except ALT and glutamate dehydrogenase in one animal. Vacuolated macrophages were observed in lymphoid tissues and spleen of HD animals. These were not observed in recovery animals. Thymic atrophy was also observed in HD dogs and correlated with lower thymic weight. This was also not observed in recovery animals.

In the kidneys of HD animals, tubular degeneration and vacuolation was observed. The basophilic tubules were observed at the end of the recovery period, but the degeneration was not observed in recovery animals. Centrilobular vacuolation was also observed in the livers of HD dogs. These correlated with gross pathology findings of lobular architecture and pale discoloration. This was not observed in recovery animals. In the lungs, vacuolated macrophages and neutrophilic infiltration were observed in HD dogs, which were not seen in recovery animals. Swollen spermatocytes in testis and epididymis were found in HD males at levels above background findings. These were also not observed in recovery animals. Cysts were also observed in the pituitary and ovaries of 2/3 HD females. Due to tubular degeneration in kidneys in the HD group, the NOAEL was concluded to be the MD of 15 mg/kg/day with $AUC_{0\text{-}24h}$ of 138 µmol.h/L and C_{max} of 9.49 µmol/L.

26-Week Dog Study (Study #528329)

In dogs orally administered brensocatib at 0 (vehicle), 2, 8, or 50 mg/kg/day for 26 weeks in a GLP study, drug-related adverse findings were evident in the 8 and 50 mg/kg dosing groups in epididymis and testis (male), lungs, lymphoid tissues, spleen, kidney, and teeth. The incidence and severity tended to be dose dependent. In epididymis, minimal to severe bilateral findings include decreased sperm cellularity, increase of cellular debris and apoptosis. In testis, minimal to severe, bilateral findings include tubular degeneration/atrophy and hypertrophy/ hyperplasia of interstitial [Leydig] cells. Minimal to mild, bilateral hypospermatogenesis was also evident in recovery animals given 50 mg/kg dose. PLD was observed in lungs, lymphoid tissues, and spleen with minimal to marked accumulations of vacuolated macrophages in all animals given 50 mg/kg dose.

In kidney, minimal to mild bilateral tubular basophilic regeneration at the corticomedullary junction was noted in animals given 50 mg/kg dose, which correlates to the increase of NAG and NAG/creatinine ratio observed in urinalysis. In addition, mild to marked periodontal inflammation, mild to moderate alveolar bone resorption/fibrosis were found in animals given 50 mg/kg dose. The drug administration was terminated for 50 mg/kg dosing animals at Week 18/19 due to serious periodontal inflammation. The most severely affected animals were euthanized at Week 18/19. Treatment was discontinued for the remainder of the 50 mg/kg dosing animals, given daily dental care, and placed in the recovery group. Periodontal disease was eliminated after 4 weeks of daily dental care and did not reoccur. The NOAEL was considered to be 2 mg/kg/day which corresponded to an $AUC_{0\text{-}24h}$ of 12.7µmol•hr/L and C_{max} of 0.948µmol/L.

39-Week Dog Study (Study #505523)

In the 39-week GLP study in dogs, animals were administered 0 (vehicle), 1, 2, 4 or 8 mg/kg/day brensocatib orally for 39 weeks with a 26-week recovery period. No drug-related adverse microscopic findings were noted. No drug-related changes in blood testosterone levels or sperm analysis parameters were noted. Minimal PLD was noted in lungs of all animals at 8 mg/kg, while the incidence in lower doses was not examined. The PLD is not considered adverse due to the minimal severity and lack of other microscopic lung findings. The NOAEL was concluded to be 8 mg/kg/day with $AUC_{0\text{-}24h}$ of 51.4µmol·hr/L and C_{max} of 4.3µmol/L.

Table 47. Summary of Brensocatib Exposures in Repeat-Dose Toxicity Studies

Study	NOAEL (mg/kg/day)	AUC (µmol.h/L)	Systemic Exposure Margin[a]
26-week rat study	9	196	20.6
26-week dog study	2	13.3	1.4
39-week dog study	8	51.4	5.4

Source: FDA Pharmacology Toxicology Reviewer table
[a] Clinical exposure in Study INS1007-201 was 4173 ng.h/mL or 9.51 µmol.h/L for 25 mg QD dosing of brensocatib
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no observed adverse effect level

Special Studies

The phototoxicity potential of brensocatib was evaluated in the neutral red uptake assay in 3T3 mouse fibroblasts exposed to brensocatib and ultraviolet radiation. The photoirradiation factor indicated that brensocatib is not phototoxic.

The lungs and kidneys of rats administered brensocatib once daily for four weeks was evaluated via TEM. Alveolar macrophages in the lungs were enlarged and increased lysosomal material accumulation was observed in male rats treated with 100 mg/kg/day brensocatib, which is consistent with phospholipidosis. The kidneys of female rats treated with 15 mg/kg/day and 100 mg/kg/day brensocatib exhibited swelling in the mitochondria and proximal tubular epithelium. This was accompanied by increased debris and cytosolic rarefaction of the proximal tubule epithelium and microvilli degeneration.

The lungs of dogs treated with brensocatib once daily for four weeks also exhibited enlarged macrophage cytoplasms in TEM images. This was also consistent with phospholipidosis.

13.1.4. Genetic Toxicology

Brensocatib was found to be negative for genotoxic potential in the in vitro bacterial reverse mutation (Ames) assay, an in vitro mouse lymphoma cell thymidine kinase locus assay, and in vivo micronucleus assay in rats.

Carcinogenicity

In a GLP 26-week carcinogenicity assessment study, CByB6F1-Tg(HRAS)2Jic mice were administered 0 (water), 0 (water with tartaric acid), 5, 15, or 50 mg/kg of brensocatib daily by oral gavage. There were 9 early mortalities- 3 in water control, 2 in vehicle control, 1 in 5 mg/kg group and 3 in 50 mg/kg group. These were not drug related and there were no statistically significant effects on mortality in either sex. A nonsignificant increase was observed in spleen hemangiosarcomas in both sexes. Further, the increase was not evident when whole body hemangiosarcomas were analyzed. The positive control (urethane) had statistically significant increases in tumors in the lung and hemangiosarcomas of the whole body. There was no evidence of brensocatib-related neoplasms in male and female mice in the 6-month study.

In a GLP 2-year carcinogenicity assessment study, Han Wistar rats were administered 0 (water with tartaric acid), 3,10, or 30 mg/kg brensocatib daily by oral gavage. A total of 173 early mortalities were observed in the study, but the differences in treatment and control groups were not statistically significant. In males, no statistically different tumors were observed. In females, stromal polyps were observed in the uterus that were borderline statistically significant in the 30 mg/kg group. However, these were below historical control levels and therefore not considered test article related. In addition, the combined incidence of stromal polyp and sarcoma

in the uterus was not significant. There was no evidence of brensocatib-related neoplasms in male and female rats in the 2-year study up to exposures 56 times MRHD on an AUC basis.

Developmental and Reproductive Toxicology

Fertility Studies

In male fertility studies integrated into the GLP 26-week repeat dose toxicity study (Study #528329), brensocatib was administered orally to male rats at 0, 3, 9, and 50 mg/kg/day once daily for ten weeks before mating with females. Brensocatib did not affect mating performance and fertility up to doses of 50 mg/kg/day in male rats. The NOAEL was determined to be 50 mg/kg/day with an $AUC_{0\text{-}24h}$ of 1460 µmol·h/L.

In a GLP study, female rats were administered orally 0, 3, 20, or 100 mg/kg/day brensocatib once daily. No drug-related effects on the estrous cycle were observed. There were no treatment related effects on female mating or mean pre-coital intervals. The fertility indices were comparable to control, and no drug-related effects were noted on female reproductive parameters. The NOAEL was concluded to be 100 mg/kg/day with an $AUC_{0\text{-}24h}$ of 1240 µmol·h/L ($AUC_{0\text{-}24h}$ obtained from the dose range finding study in pregnant rats [Study #497631]).

Embryofetal Development Studies (Study# 497825 and # 497626)

In the GLP combined fertility and embryo-fetal development study in female rats, animals were orally administered 0, 3, 20, or 100 mg/kg/day brensocatib from 2 weeks prior to pairing for mating to up to gestation day (GD) 16. No drug-related adverse maternal toxicities were noted. Decreases in body weight gain and food consumption during the first week of dosing were fully recovered during the second week. Drug-related adverse skeletal malformation of bent scapula was observed in fetuses from pregnant dams administered 100 mg/kg/day brensocatib (4 of 110 fetuses, 3.7%). The variation wavy ribs were present at moderate severity in 5 of 134 fetuses (3.8%) from pregnant dams administered 20 mg/kg/day. At a maternal dose of 100 mg/kg/day, the wavy rib incidence of moderate severity increased to 10 of 110 fetuses (9.2%) and progressed to severe in 2 fetuses (1.8%). Other drug-related skeletal variations included unilateral/bilateral malpositioned caudal pelvic girdle, full/short cervical/thoracolumbar supernumerary rib, and a transient effect on ossification of various sites at 20 mg/kg/day and 100 mg/kg/day. The NOAEL for developmental toxicity was determined to be 20 mg/kg/day with an $AUC_{0\text{-}24h}$ of 403 µmol·h/L. The NOAEL for maternal toxicity was the highest dose administered, 100 mg/kg/day with an $AUC_{0\text{-}24h}$ of 1240 µmol·h/L.

In the GLP embryo-fetal development study in female rabbits orally administered 0, 5, 15, and 50 mg/kg/day brensocatib from GD 7 to GD 19, substantial (>50%) and statistically significant decreases of body weight gain and food consumption were noted at 15 and/or 50 mg/kg during gestation period. These were considered drug-related and adverse due to the magnitude and the timing (the second half course of drug treatment). Thus, the NOAEL for maternal toxicity was considered 5 mg/kg/day with correlated GD 16 $AUC_{0\text{-}24h}$ of 15.1µmol·h/L. There were no drug-related adverse developmental toxicities at up to 50 mg/kg. Thus, the NOAEL was considered 50 mg/kg/day for developmental toxicity with correlated GD 16 $AUC_{0\text{-}24h}$ of 195µmol·h/L in female rabbits.

Pre- and Postnatal Development Study (Study #00335001)

In the GLP PPND study in pregnant F0 rats, animals were orally administered 0, 3, 9 or 20 mg/kg/day brensocatib from GD 6 to lactation Day 20. For F0 animals, no drug-related maternal toxicity or effect on reproductive parameters was noted. For F1 pups, no drug-related effects on postnatal survival, body growth, puberty, startle response, motor activity, learning or memory performance were noted from birth to prior to weaning. Following weaning and subsequent mating, decreased mean body weight gain was noted during GD 0 through 15 in the F1 pups from F0 dams at 20 mg/kg. Since adjusted body weight gain was not determined, it cannot be concluded whether the decreases were random or due to possible changes in gravid uterine weight. No drug related changes of reproductive performance or reproductive parameters were noted for F1 pups. No drug-related changes in the F2 embryonic survival were noted. The NOAEL was determined to be 20 mg/kg/day with an $AUC_{0\text{-}24h}$ of 163 µmol·h/L.

Table 48. Brensocatib Exposure Margins in Reproductive and Development Toxicity Studies

Study		NOAEL (mg/kg/day)	AUC (µmol·h/L)	Systemic Exposure Margin[a]
Fertility	Male rat[b]	50	1460	154
	Female rat[c]	100	1240	128
EFD rat	Maternal[c]	100	1240	128
	Development[d]	20	403	42
EFD rabbit[e]	Maternal	5	15.1	1.6
	Development	50	195	20
PPND rat[f]		20	163	17

Source: FDA Pharmacology Toxicology Reviewer table
[a] Clinical exposure in Study INS1007-201 was 4173 ng·h/mL or 9.5 µmol·h/L for 25 mg QD dosing of brensocatib
[b] $AUC_{0\text{-}24}$ for male fertility is obtained from fertility studies incorporated into the 26-week repeat dose toxicity study (Study #528313)
[c] $AUC_{0\text{-}24}$ for female rats was obtained from DRF study in pregnant rats (Study #497631)
[d] $AUC_{0\text{-}24}$ from Study #497825
[e] $AUC_{0\text{-}24}$ for rabbits was obtained from Study# 497626
[f] $AUC_{0\text{-}24}$ from PPND study in rats (Study# 00335001).
Abbreviations: AUC, area under the concentration-time curve; EFD, Embryo-fetal development; NOAEL, no observed adverse effect level; PPND, Pre- and Postnatal Development

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Impurities

13.2.1.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title: Reverse Mutation Assay using Bacteria (Salmonella typhimurium and Escherichia coli) - Enhanced Ames Test -with (b) (4)

(b) (4)

Table 49. Information, Study STURS24AA0598-1

Parameter	Information
Study no.	STURS24AA0598-1
Study report location	SD3 Nonclinical Information Amendment
Conducting laboratory and location	(b) (4)
GLP compliance	Yes
Drug impurity, lot #, and % purity	(b) (4) %

Source: FDA Pharmacology Toxicology Reviewer table
Abbreviation: GLP, good laboratory practice

Table 50. Methods, Study STURS24AA0598-1

Parameter	Information
Strains	*Salmonella typhimurium* tester strains TA100, TA1535, TA98, TA1537 and *E. coli* WP2 uvrA (pKM101)
Concentrations in definitive study	0.316- 5000µg
Basis of concentration selection	Pre-dosing experiment for solubility and toxicity
Negative control	DMSO
Positive control	Sodium azide (10µg/plate for TA100 and TA1535), 4-nitro-o-phenylene-diamine (10µg/plate for TA98; 40µg/plate for TA1537), methylmethanesulfonate (1µL/plate for E. coli WP2 uvrA (pKM101)), 2-aminoanthracene (2.5µg/plate for TA98, TA100 and TA1535; 10µg/plate for TA1537 and E. coli WP2 uvrA (pKM101)), (b) (4) (2500µg/plate), and (b) (4) (500µg/plate)
Formulation/vehicle	DMSO
Incubation & sampling time	For the preincubation method, tester strains were incubated with (b) (4) or control, with or without S9 mix. The S9 mix was prepared from rat or hamster liver homogenate and the concentration was 30%, which is appropriate for an Enhanced Ames Test (EAT). After 30 min preincubation, overlay agar was added and the mixture poured onto agar plates. Plates were incubated for at least 48h at 37ºC before colony counting.
Comment on study validity	The strains selected for testing are appropriate and positive controls yielded expected results. Therefore, the study is deemed valid.

Source: FDA Pharmacology Toxicology Reviewer table
Abbreviations: C, Celsius; DMSO, dimethyl sulfoxide; EAT, Enhanced Ames Test

Results

An enhanced Ames test (EAT) was performed to determine the mutagenic potential of (b) (4) (b) (4) For the assay to be an EAT, it should be conducted in the absence of a post-mitochondrial fraction (S9), and also in the presence of 30% rat liver S9, as well as 30% hamster liver S9. Precipitation was observed at ≥31.6µg (b) (4) with or without S9 fraction across all strains. Toxicity was observed in TA98 strain at 5000µg/plate and in TA1535 strain at

≥1000µg/plate in the absence of metabolic activation. With rat liver S9, toxicity was observed at ≥316µg/plate for strains TA100 and TA1537. In repeat confirmation experiment, toxicity was observed at concentrations as low as 10µg/plate for TA1535. With hamster S9, toxicity was observed at ≥2000µg/plate in TA1537 strain and ≥316µg/plate.

No relevant increases in colony numbers were observed for any of the strains with or without metabolic activation when assuming a mutation factor threshold value of 3.0 without S9 and 2.0 with S9. The positive controls exhibited a mutation factor higher than the negative controls, test article and the threshold value set for the experiment. Therefore, (b) (4) is considered negative in the EAT.

13.2.1.2. In Vitro Assays in Mammalian Cells

Study Title: In Vitro Mammalian Cell Gene Mutation Assay (Thymidine Kinase Locus/tk+/-) in L5178Y Mouse Lymphoma Cells With (b) (4)
(b) (4)

Table 51. Information, Study STUGC24AA2299-2

Parameter	Information
Study no.	STUGC24AA2299-2
Study report location	SD3 Module 4.2.3.7.6
Conducting laboratory and location	(b) (4)
GLP compliance	Yes
Impurity, lot #, and % purity	(b) (4) %

Source: FDA Pharmacology Toxicology Reviewer generated table
Abbreviation: GLP, good laboratory practice

Table 52. Methods, Study STUGC24AA2299-2

Parameter	Information
Cell line	Mouse lymphoma L5178Y tk+/- 3.7.2C
Concentrations in definitive study	Short term(-): 0.00039, 0.00078, 0.00156, and 0.00313 mg/mL Short term(+): 0.00078, 0.00156, 0.00313, and 0.00625 mg/mL Long term experiment: 0.00313, 0.00625, 0.0125, and 0.025 mg/mL
Basis of concentration selection	Dose range experiment for toxicity and precipitation
Negative control	DMSO
Positive control	Without metabolic activation- ethyl methanesulfonate (EMS) and methyl methanesulfonate (MMS) With metabolic activation- benzo[a]pyrene
Formulation/vehicle	DMSO
Incubation & sampling time	Cell cultures were exposed to (b) (4) in the presence and absence of S9 for 4 hours or 24 hours. Following treatment, cells were washed and cultured in suspension for a 48-hour expression period. After the expression period, the relative cloning efficiency was determined by seeding new

	plates and incubating cultures for another 7 days. For mutation analysis, cells were seeded and incubated for 14 days.
Comment on study validity	The study is considered valid as it includes cytotoxicity data, plating efficiency determination, colony counts and mutant frequencies for treated and control cultures and mutant colony sizing. Positive controls had higher GEF than the established value as well as increased colony counts.

Source: FDA Pharmacology Toxicology Reviewer table
Abbreviations: C, Celsius; DMSO, dimethyl sulfoxide; GEF, global evaluation factor; MMS, methyl methanesulfonate

Results

A dose ranging experiment was performed at concentrations between 0.000195 mg/mL and 0.5 mg/mL. Precipitation was observed at ≥0.00313 mg/mL without metabolic activation and ≥0.00625 mg/mL with metabolic activation in short term experiments and at ≥0.025 mg/mL in long term experiments. In both short-term experiments with or without metabolic activation and the long-term experiment, no significant toxicities were observed with test article treatment. The mutagenicity was compared to the global evaluation factor (GEF), which is defined as the mean of the negative/vehicle mutant frequency plus one standard deviation where data are gathered from ten laboratories. For the microwell format the GEF is 126 mutants / 10^6 cells. The positive controls were greater than the GEF but the test article values for GEF were well below this limit. The positive controls also exhibited a significant increase in colony formation indicating clastogenicity in the positive control. Therefore, (b) (4) is considered non-mutagenic.

Integrated Analysis of (b) (4)

(b) (4) identified in the drug product. Following the CPCA methodology, a Potency Score of 2 was assigned to (b) (4) corresponding to an AI limit of (b) (4) ng/day. Therefore, the Applicant (Insmed Inc.) conducted additional studies to evaluate the risk posed by this (b) (4) and justify higher limits. Specifically, they have performed an EAT and an in vitro mammalian cell gene mutation assay in mouse lymphoma cells to investigate the mutagenicity of (b) (4) As stated above, (b) (4) (b) (4) did not exhibit mutagenic effect in either assay. Additionally, the Applicant has evaluated the in vitro metabolism of (b) (4) in human liver microsomes (HLM) as well as rat liver S9 fraction induced with phenobarbital or β-naphthoflavone (in the presence or absence of NADPH). Five (5) µM of (b) (4) in HLM or rat S9 did not produce any further (b) (4) metabolites. The metabolism chiefly affected the (b) (4) (b) (4) a positive control compound, was also subjected to similar metabolic conditions to confirm the activity of the hydrolytic enzymes.

FDA computational toxicology and metabolism experts concluded that the presence of the (b) (4) (b) (4) (b) (4) (> (b) (4) g/mol) may result in lower carcinogenic potency than suggested by the CPCA potency category 2 assignment for the impurity. (b) (4) (b) (4) (b) (4) DNA-reactivity of these species is

therefore less favorable compared to (b) (4). Furthermore, the resulting (b) (4) species that could potentially form via (b) (4) species is of (b) (4), also leading to reduced potential for DNA-reactivity compared to that formed from (b) (4) Therefore, the absence of a positive response in an enhanced bacterial mutagenicity assay is not unexpected despite the observation that (b) (4) products may be formed in metabolism studies.

In summary, (b) (4) is non-mutagenic and is unlikely to form further metabolites that could enhance overall mutagenicity. Therefore, a drug product specification limit of (b) (4) ng/day is justified.

Overall, the Applicant followed the recommendations of the ICH scientific guideline *ICH M7(R2) Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (September 2023b) and evaluated the mutagenic potential of impurities based on literature, internal databases, and in silico assessment including multiple computer aided structure evaluation and deductive estimation of risk from existing knowledge. Overall, the proposed impurity specifications are acceptable and there are no outstanding nonclinical safety concerns.

Other identified impurities are appropriately controlled per the ICH guidance for industry *ICH Q3A Impurities in New Drug Substances* (June 2008), ICH scientific guideline *ICH Q3B(R2) Impurities in New Drug Products* (June 2006), USP Guidelines or qualified in nonclinical toxicology studies.

14. Clinical Pharmacology

14.1. In Vitro Studies

Sixteen in vitro study reports were submitted to characterize the protein binding, metabolism, and DDI potential of brensocatib. All in vitro studies were reviewed and are summarized in this section. Note that, in this review, drug code names INS1007, AZD7986, and AZ13661057 are also used to refer to brensocatib. Also note that following QD dosing in subjects with NCFB in Study 301, the mean steady-state C_{max} of brensocatib is 85.4 ng/mL (0.19µM) and 259 ng/mL (0.59µM) for 10 mg and 25 mg, respectively, and the steady-state trough concentration is up to 57.5 ng/mL (0.13µM) and 157 ng/mL (0.36µM), for 10 mg and 25 mg, respectively.

Table 53. Summary of In Vitro Studies

Characteristic	Report ID: Title	Conclusions
Distribution	ADME-AZS-Wave4-130621: The Determination of the In Vitro Binding of AZ13661057 to Plasma Proteins in the Mouse, Rat, Rabbit, Dog and Human	The average percentage of unbound drug was 16.5% in mouse, 22.7% in rabbit, 29.7% in dog and 12.8% (in human over AZ13661057 concentration range of 0.1 to 100µmol/L.
	BE00090 1_ 12: AZD7986: In Vitro Covalent Binding of [^{14}C]-Labeled AZD7986 (C4C]-AZ13661057) to Human Hepatic Proteins in Human Hepatocyte Incubations	In vitro covalent binding was observed in 4-hour incubation of 10µM [^{14}C] AZD7986 in cryopreserved human hepatocytes.

Characteristic	Report ID: Title	Conclusions
Metabolism	BE000083-57: AZD7986: In Vitro Metabolism of [^{14}C]AZD7986 in Hepatocytes from Human, Rat and Dog	After 240 minutes incubation of [^{14}C]AZD7986 in cryopreserved hepatocytes at a total concentration of 40µmol/L, a total of two metabolites were detected by radioactivity detection, two in rat hepatocyte incubates, one in dog hepatocyte incubates and none in human hepatocyte incubates. A total of five metabolites were detected by MS, all five metabolites were found in rat and dog, four metabolites were found in human hepatocyte incubates. The major metabolic pathways were oxidations on the oxazepane ring, but N-demethylation was also observed.
	BJAA-0003-DV-HB: Determination of Stability of INS1007 in CD-1 Mouse, Sprague-Dawley Rat, Beagle Dog, and Human Intestine Microsomes	After 120-minute incubation of INS1007 (4µM) in the presence of CD-1 mouse, Sprague-Dawley rat, beagle dog and human intestine microsomes, the percentage of INS1007 remaining was 95%, 102%, 99% and 100%, respectively.
	ADME-AZS-Wave3-140531: Determination of the Human Cytochrome P450 Enzymes Involved in the Metabolism of AZ13661057(AZD7986)	AZD7986 (2µmol/L) was incubated with bactosomes prepared from E. Coli bacteria which express 10 human CYP isoforms. CYPs 3A4 and 3A5 were found to be the predominant CYP isoforms involved in the metabolism of AZD7986, accounting for 39% and 58% of its metabolism, respectively. Both CYPs 2D6 and 2C8 account for <2% of CYP-mediated metabolism. CYPs 1A2, 2A6, 2B6, 2C9, 2C19 and 2E1 were not shown to metabolize AZD7986.
DDI potential-CYP inhibition	ADME-AZS-Wave3-140529: Assessment of the Cytochrome P450 Inhibition Potential of AZ13661057 (AZD7986) in Human Liver Microsomes for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5	AZD7986 (0.1, 0.3, 1, 3, 10, 30µM) was incubated with human liver microsomes in the presence of CYP enzyme marker substrates and NADPH. Minor inhibition of CYPs 2D6 and 3A4/5 activity by AZD7986 was observed, but not sufficient to determine IC_{50} value (i.e., IC_{50}>30µM). There was no evidence that AZD7986 inhibited CYPs 1A2, 2C9 and 2C19 over the concentration range tested.
	ADME-AZS-Wave3-140530: Assessment of the Cytochrome P450 Time Dependent Inhibition Potential of AZ13661057 (AZD7986) in Human Liver Microsomes	AZD7986 (10 and 50µM) was incubated with human liver microsomes in the presence and absence of NADPH, followed by10-fold dilution and coincubation with CYP enzyme marker substrates and NADPH. No time dependent inhibition was observed for AZD7986 on CYPs 1A2, 2C9, 2C19, 2D6, 3A4/5.
	ADME-AZS-Wave3-140613: Assessment of the Cytochrome P450 Inhibition Potential of AZ13661057 (AZD7986) in Human Liver Microsomes for CYP2A6, CYP2B6, CYP2C8, CYP2E1 and CYP3A4/5	AZD7986 (0.1, 0.3, 1, 3, 10 and 30µM) was incubated with human liver microsomes in the presence of CYP enzyme marker substrates and NADPH. AZD7986 showed inhibition of CYP2B6 activity (17.6% inhibition) and CYP3A4/5 activity (22.9% inhibition) at 30µM, but no IC_{50} value could be determined (i.e., IC_{50}>30µM). There was no evidence that AZD7986 inhibited CYPs 2A6, 2C8 and 2E1 over the concentration range tested.

Characteristic	Report ID: Title	Conclusions
DDI potential-CYP induction	PR13028/PR13074/ PR13101: Evaluation of induction properties of AZ13661057 (AZD7986) on cytochromes P450 mRNA Level: in vitro experiments using HepaRG cells	Human hepatocyte cell line HepaRG were exposed to AZD7986 at 0.0002-30μM for 24 hours to investigate the induction potential of AZD7986 on CYP (1A2, 2B6 and 3A4) mRNA content. The same procedure was repeated in 3 studies. Induction of CYP mRNA was observed in 1 of 3 studies for CYP1A2, in 2 of 3 studies for CYP2B6, and in all 3 studies at 3, 10, and 30μM for CYP3A4 in a concentration dependent manner.
	8492164: Evaluation of Cytochrome P450 Induction Following Exposure of Primary Cultures of Human Hepatocytes to Brensocatib (INS1007)	Hepatocytes from three human donors were separately incubated with brensocatib (2.2, 7, 22, 70, 220, 700, and 2200 ng/mL), a prototypical inducer for each enzyme, two non-inducers, and appropriate solvent control for 72 hours to analyze mRNA expression and enzyme activities. Brensocatib was identified as an inducer of CYP3A4 gene expression and CYP3A4/5 enzyme activity, but not an inducer for CYPs 1A2, 2B6, 2C8, 2C9, or 2C19. The calculated relative induction score (RIS) (0.116) and the predicted ratio (R3) of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and presence of an inducer (0.512) values for CYP3A4 suggest that brensocatib is a CYP3A4 inducer and has the potential for in vivo induction of CYP3A4.

Characteristic	Report ID: Title	Conclusions
DDI potential-transporter	Insmed-01: In vitro Interaction Studies of Brensocatib with human BCRP and MDR1 Efflux (ABC) Transporters, and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters	In vitro assay using MDCKII-BCRP and Abcb1KO-MDCKII-MDR1 cell monolayers indicated that brensocatib is a BCRP substrate with the highest net efflux ratio of 20.65 at 1μM concentration, and likely a MDR1 (i.e., P-gp) substrate. In vitro assay using MDCKII and HEK293 cells indicated that brensocatib is not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 (SLC).
	BJAA-0002-DV-PB: INS1007 Permeability in Human Caco-2 Cells	The permeability of INS1007 using human Caco-2 cells were assessed with 10μM INS1007 with and without verapamil (non-specific P-gp inhibitor) and itraconazole (specific P-gp inhibitor). The efflux ratio of INS1007 was 3.86 and this efflux was inhibited 54% and 38% by 25μM verapamil and 10μM itraconazole respectively, indicating that INS1007 is a P-gp substrate.
	16AZTrPIS1: Assessment of AZD7986 as an inhibitor of the human transporter proteins OATP1B3, OATl, OAT3, MATEl, MATE2K and OCT2	Using in vitro transfected test systems, AZD7986 inhibited probe substrate transport via MATE1 (IC_{50}=11.5μM), and MATE2K (IC_{50}=15.3μM), but not via OAT1 and OCT2. The IC_{50} for OAT3 and OATP1B3 would be greater than 100μM.
	BE000458-17 AZ 13661057: Assessment of the Human BCRP Inhibition Potential of AZ13661057 (AZD7986) in Caco-2 Cells	Using Caco-2 cells, AZD7986 inhibits [^{3}H]-rosuvastatin (probe substrate) transport via human BCRP, with an apparent IC_{50} value of 39.2μM.
	BE000685-13_AZ13661057: Assessment of the OATPlBl Inhibition Potential of AZ13661057 (AZD7986) in HEK293-0ATP1Bl Cells	Using HEK293-OATP1B1 cell system, AZD7986 inhibited OATP1B1 mediated transport of [^{3}H]Estradiol 17β glucuronide (probe substrate) in a concentration-dependent manner with an apparent IC_{50} value of 49μM.
	Pgp inhib_l2Sepl3_AZ13661057: Assessment of the Human P-gp Inhibition Potential of AZ13661057 (AZD7986) in MDCKII-MDRl Cells	Using MDCKII cell system, the apparent permeability (Papp) values for digoxin (probe substrate) remained comparable in the absence or presence of AZD7986 (300μM). Therefore, AZD7986 does not inhibit P-gp over the concentration range tested (1-300μM).

Source: FDA summary
Abbreviations: ADME, absorption, distribution, metabolism, excretion; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DDI, drug-drug interaction; MDRI, multidrug resistant infections; mRNA, messenger ribonucleic acid; MS, mass spectrometry; RIS, relative induction score

14.2. In Vivo Studies

This NDA submission consists of 11 clinical and clinical pharmacology studies, including 9 phase 1 studies conducted in healthy subjects, 1 phase 2 study, and 1 phase 3 study. Later phase studies were conducted in subjects with NCFB (Table 54). In addition, 5 reports for population PK analysis, exposure-response analysis, and PBPK analysis were submitted.

Brensocatib was administered as an immediate release film-coated tablet formulation in the phase 2 (phase 2 tablet) and phase 3 (phase 3 tablet) trials as well as most of the phase 1 studies. The proposed to-be-marketed drug product (10 mg and 25 mg tablets) is identical to the drug

products used in phase 2 and phase 3 trials with respect to the core tablet formulation, shape, and size. (b) (4)

(b) (4)

Comparison of dissolution profiles was proposed to bridge the phase 2, phase 3, and to-be-marketed drug products. We defer to the CMC and biopharm teams regarding the adequacy of formulation bridging.

Note that in this review, drug code names INS1007, AZD7986, and AZ13661057 are also used to refer to brensocatib.

Table 54. Summary of Clinical Pharmacology Studies

Study	Design	Study Formulation	Dosing Regimen
D6190C00001	Phase 1, FIH, SAD/MAD, food effect study in healthy subjects	Oral solution (1-50 mg/mL)	• SD: 5, 15, 35, 50, 65 mg • MD: 10, 25, 40 mg/day, up to 28 days
D6190C00003	Phase 1, DDI (CYP3A, P-gp inhibitor) study in healthy subjects	Oral solution (1-50 mg/mL)	• SD 25 mg
INS1007-101	Phase 1, PK, PD, food effect study in healthy Japanese and Caucasian subjects	Phase 2 tablet (10, 15, 25 mg)	• SD: 10, 25, 40 mg • MD: 10, 25, 40 mg QD, 28 days
INS1007-102	Phase 1 PK study in subjects with or without renal impairment	Phase 3 tablet (25 mg)	• SD 25 mg
INS1007-103	Phase 1, mass balance study in healthy subjects	Oral solution ([^{14}C]-brensocatib containing ~100µCi)	• SD: 40 mg
INS1007-104	Phase 1, thorough QT/QTc study in healthy subjects	Phase 3 tablet (40 mg)	• SD: 80, 120 mg
INS1007-105	Phase 1 PK study in subjects with normal hepatic function or with hepatic impairment	Phase 3 tablet (25 mg)	• SD 25 mg
INS1007-106	Phase 1, DDI (CYP3A inducer, PPI) study in healthy subjects	Phase 3 tablet (25 mg)	• SD 25 mg
INS1007-109	Phase 1, DDI (CYP3A, P-gp inhibitor) study in healthy subjects	Phase 3 tablet (25 mg)	• SD 25 mg
(b) (4)			
INS1007-301	Phase 3 efficacy study in subjects with NCFB	Phase 3 tablet (10, 25 mg)	• 10, 25 mg QD, 52 weeks

Source: Table 1 of Summary of Clinical Pharmacology Studies, Section 3 of Tabular Listing of Clinical Studies, Table 2 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Phase 2 tablets were manufactured by (b) (4) Phase 3 tablets were manufactured by Patheon, Canada (b) (4).
Abbreviations: DDI, drug-drug interaction; FIH, first-in-human; MAD, multiple ascending dose; MD, multiple dose; NCFB, non-cystic fibrosis bronchiectasis; PD, pharmacodynamic; PK, pharmacokinetic; PPI, proton pump inhibitor; QD, once daily; QT, QT interval; QTc, QT interval corrected by heart rate; SAD, single ascending dose; SD, single dose

Thiocyanate (M8) is the only major circulating metabolite of brensocatib in human plasma, accounting for 51% total AUC. It is an endogenous molecule with GRAS status. Thiocyanate plasma concentrations have been measured in Studies INS 1007-201 (Report VV-NC-000801), INS 1007-102 (Report VV-NC-000802), INS 1007-104 (Report VV-NC-000803), and INS 1007-105 (Report VV-NC-000892) and will also be reviewed in this section.

14.2.1. Study D6190C00001

Title

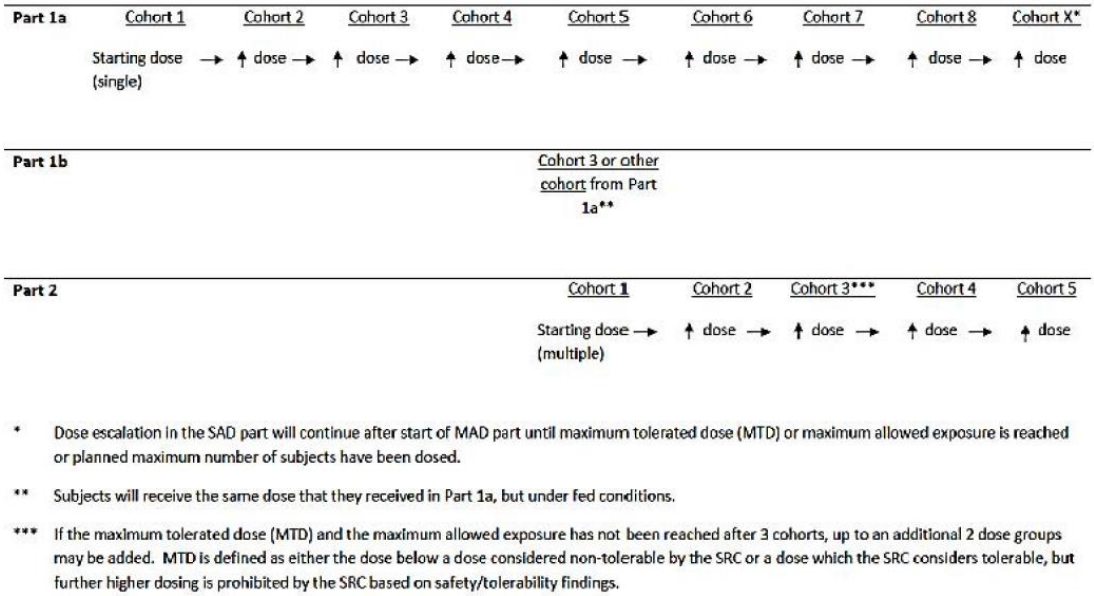
A phase 1, randomized, single-blind, placebo-controlled, 2-part study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and food effect of single and multiple oral doses of AZD7986 in healthy volunteers

Study Design

This is a phase 1 FIH study in healthy subjects and was conducted in 2 parts (Part 1a single ascending dose [SAD]; Part 1b food effect; and Part 2 multiple ascending dose [MAD]).

- Part 1a (SAD): Part 1a was a randomized, single-blind (subject and investigator blind), placebo-controlled study. Up to 5 ascending dose levels with the starting dose of 5 mg were planned and sentinel dosing was employed. In each cohort, 6 subjects were randomized to receive AZD7986 and 3 subjects received placebo. Each subject received a single dose on Day 1 under fasted conditions.
- Part 1b (food effect): Subjects of Cohort 3 from Part 1a returned to the clinic after a washout period of at least 7 days and received another single oral dose of AZD7986. Subjects were dosed with AZD7986 of the same dose strength (i.e., 35 mg) as in Part 1a within 30 minutes after the start and 5 minutes after the completion of a high fat breakfast.
- Part 2 (MAD): Part 2 of the study was a randomized, single-blind (subject and investigator blind), placebo-controlled, MAD study. Once daily dosing was administered in the morning from Day 1 to Day 21 (or Day 28).

Figure 20. Study Design, Study D6190C00001



* Dose escalation in the SAD part will continue after start of MAD part until maximum tolerated dose (MTD) or maximum allowed exposure is reached or planned maximum number of subjects have been dosed.

** Subjects will receive the same dose that they received in Part 1a, but under fed conditions.

*** If the maximum tolerated dose (MTD) and the maximum allowed exposure has not been reached after 3 cohorts, up to an additional 2 dose groups may be added. MTD is defined as either the dose below a dose considered non-tolerable by the SRC or a dose which the SRC considers tolerable, but further higher dosing is prohibited by the SRC based on safety/tolerability findings.

Source: Figure 9-1 of Study D6190C00001 CSR
Abbreviations: MAD, multiple ascending dose; MTD, maximum tolerated dose; SAD, single ascending dose

Study Formulation

Oral solution (1-50 mg/mL).

Sampling

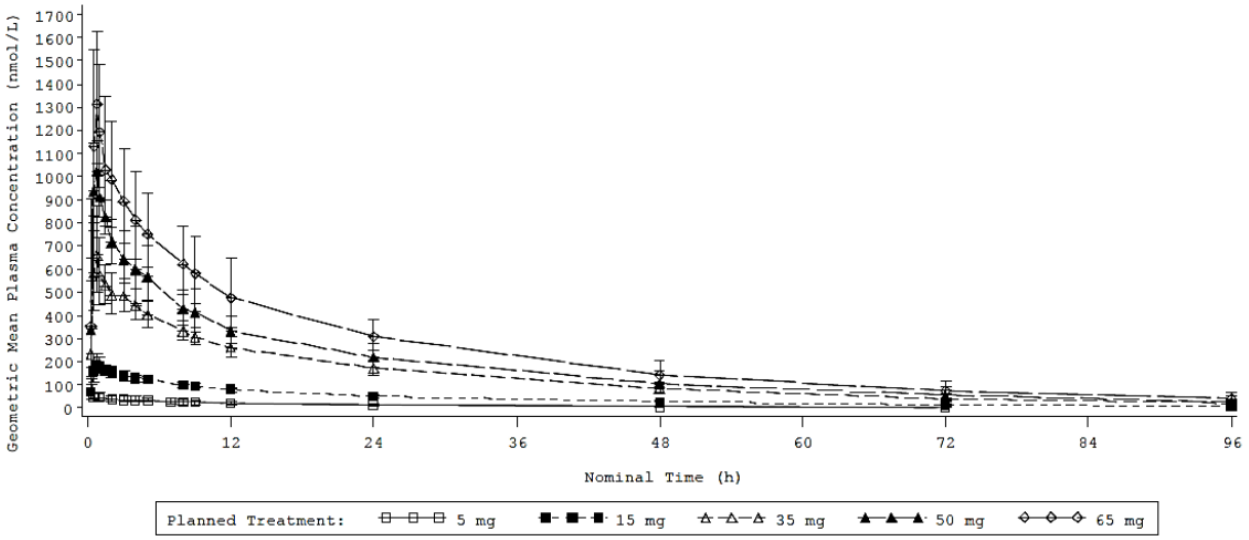
Plasma samples was collected predose (0 hour) and at 0.5, 1, 2, 3, 4, 5, 7, 8, 9, 12, 24, 48, 72 and 96 hours postdose.

Results

Part 1a (SAD)

Following single dose administration of AZD7986 oral solution at 5, 15, 35, 50 and 65 mg to healthy subjects under fasted conditions, the median T_{max} ranged from 0.5 to 0.75 hours. C_{max} and AUC appeared to increase more than dose proportionally between 5 mg and 35-mg doses, but proportionally over 35-mg to 65-mg dose range.

Figure 21. Geometric Mean Plasma Concentrations (nmol/L) of AZD7986 vs. Time Following Single AZD7986 Administration at 5, 15, 35, 50 and 65 mg in Healthy Subjects Under Fasted Conditions



Source: Adapted from Figure 11-1 of Study D6190C00001 CSR
Abbreviation: h., hour

Table 55. Summary of AZD7986 PK Parameters by Treatment in Healthy Subjects in Part 1a SAD

Parameter (Unit)		AZD7986 5 mg (n = 6)	AZD7986 15 mg (n = 6)	AZD7986 35 mg (n = 6)	AZD7986 50 mg (n = 6)	AZD7986 65 mg (n = 6)
$AUC_{(0\text{-last})}$ (h·nmol/L)	Geometric Mean	839.0*	3855	12430	16470	22880
	CV%	(48.3)	(9.3)	(18.3)	(22.7)	(21.2)
AUC (h·nmol/L)	Geometric Mean	915.3	4165	13230	17590	24710
	CV%	(46.1)	(10.8)	(19.6)	(25.2)	(21.5)
C_{max} (nmol/L)	Geometric Mean	50.74	202.3	668.1	1035	1358
	CV%	(47.2)	(16.0)	(26.7)	(11.5)	(24.2)
t_{max} (h)	Median	0.50	0.75	0.75	0.64	0.75
	Min, Max	(0.50, 1.00)	(0.53, 2.00)	(0.53, 1.50)	(0.52, 0.75)	(0.52, 1.98)
$t_{1/2\lambda z}$ (h)	Arithmetic Mean	19.96	25.92	23.80	24.52	25.50
	SD	(3.416)	(4.452)	(3.328)	(5.836)	(7.254)
MRT (h)	Arithmetic Mean	27.03	34.94	32.15	32.19	33.76
	SD	(4.373)	(5.863)	(5.003)	(8.360)	(10.35)
CL/F (L/h)	Arithmetic Mean	14.23	8.606	6.395	6.938	6.371
	SD	(7.577)	(0.9321)	(1.281)	(1.777)	(1.317)
Vz/F (L)	Arithmetic Mean	385.1	318.8	215.8	236.8	231.0
	SD	(129.6)	(46.72)	(29.62)	(39.64)	(67.56)

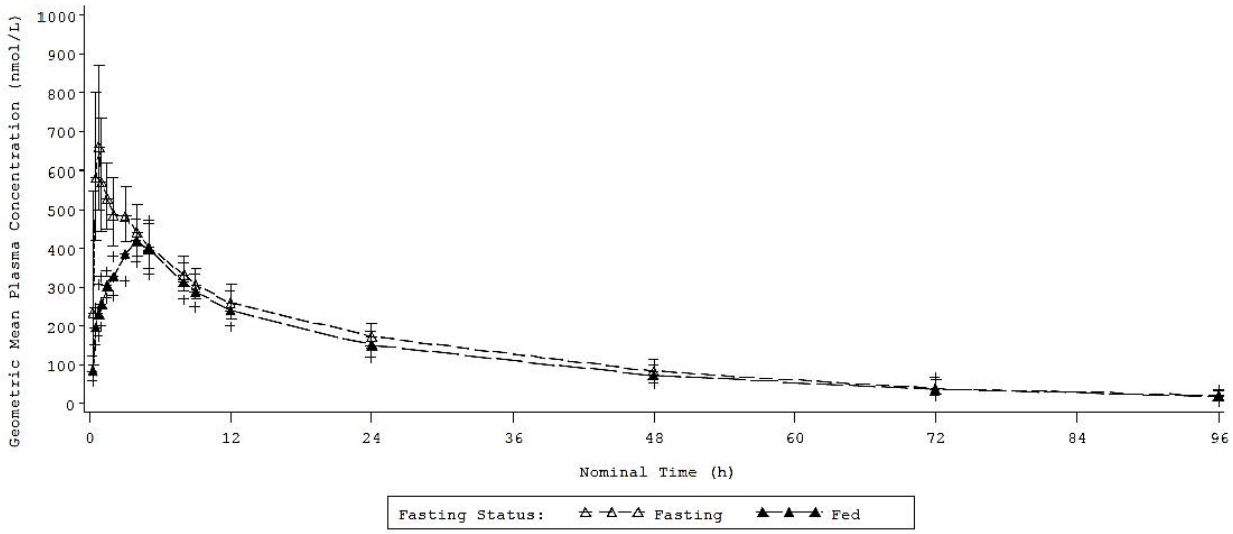
*t_{last} was nominal 48 hours for one subject, 72 hours for 4 subjects and 96 hours for one subject, therefore may not be comparable with 15 to 65 mg dose levels.

Source: Table 11-2 of Study D6190C00001 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; SAD, single ascending dose; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Part 1b (Food Effect)

Following single dose administration of AZD7986 oral solution at 35 mg to healthy subjects immediately following a high fat breakfast, the median T_{max} was delayed from 0.75 hours under fasted conditions to 4 hours under fed conditions. C_{max} and AUC under fed conditions were reduced by 36% and 9%, respectively, compared to those under fasted conditions.

Figure 22. Geometric Mean Plasma Concentrations (nmol/L) of AZD7986 vs. Time Following a Single 35-mg Dose of AZD7986 in Healthy Subjects Under Fasted or Fed Conditions



Source: Adapted from Figure 11-5 of Study D6190C00001 CSR
Abbreviation: h, hour

Table 56. Summary of AZD7986 PK Parameters Following a Single 35-mg Dose of AZD7986 in Healthy Subjects Under Fasted or Fed Conditions

Parameter (Unit)		AZD7986 35 mg fed (n = 5)	AZD7986 35 mg fasted (n = 6)	Ratio of fed/fasted
$AUC_{(0\text{-last})}$ (h·nmol/L)	Geometric Mean	10790	12430	0.868
	CV%	(20.2)	(18.3)	-
AUC (h·nmol/L)	Geometric Mean	11550	13230	0.873
	CV%	(22.6)	(19.6)	-
C_{max} (nmol/L)	Geometric Mean	434.8	668.1	0.651
	CV%	(14.0)	(26.7)	-
t_{max} (h)	Median	4.00	0.75	-3.25*
	Min, Max	(3.00, 4.98)	(0.53, 1.50)	-
$t_{1/2\lambda z}$ (h)	Arithmetic Mean	24.24	23.80	-
	SD	(4.259)	(3.328)	-
MRT (h)	Arithmetic Mean	33.73	32.15	-
	SD	(6.429)	5.003	-
CL/F (L/h)	Arithmetic Mean	7.363	6.395	-
	SD	(1.810)	(1.281)	-
Vz/F (L)	Arithmetic Mean	249.5	215.8	-
	SD	(24.96)	(29.62)	-

* difference of fed minus fasted shown.

Source: Table 11-5 of Study D6190C00001 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; SAD, single ascending dose; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 57. Statistical Analysis of the Effect of a High Fat Breakfast on AZD7986 Pharmacokinetics Following a Single 35 mg AZD7986 Dose in Healthy Subjects

Parameter (unit)	Fasting Status	N	n	Geometric LS mean	95% CI	Pairwise comparisons Pair	Ratio (%)	90% CI
C_{max} (nmol/L)	Fasting	5	5	677.9	(510.8, 899.7)			
	Fed	5	5	434.8	(327.6, 577.0)	Fed/Fasting	64.14	(55.07, 74.70)
AUC (h*nmol/L)	Fasting	5	5	12730	(9840, 16470)			
	Fed	5	5	11550	(8927, 14940)	Fed/Fasting	90.72	(83.72, 98.31)

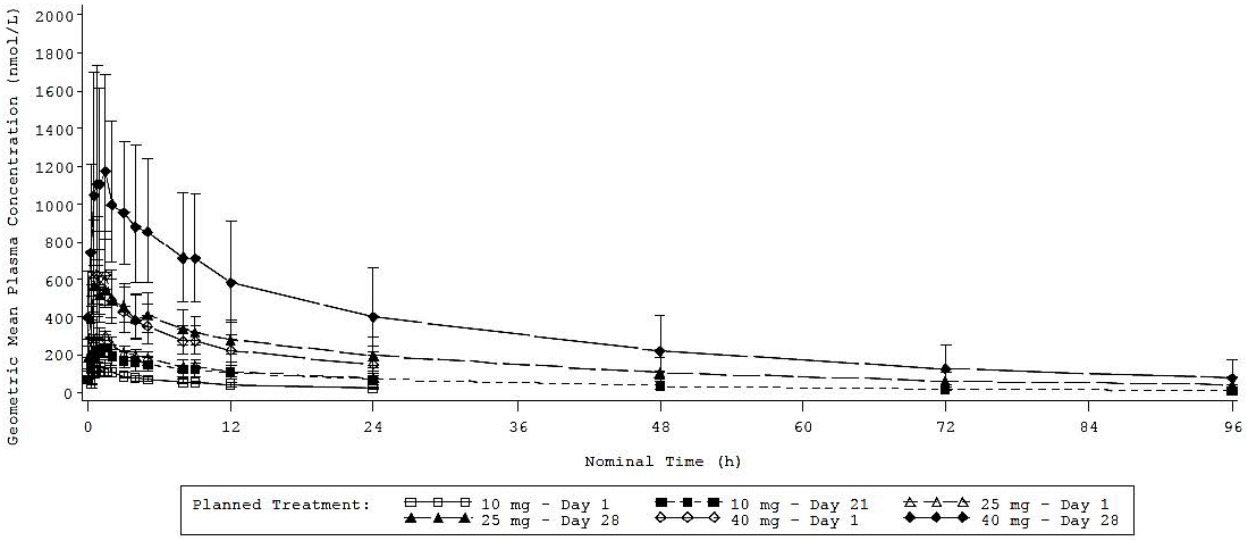
Source: Table 11-6 of Study D6190C00001 CSR
Results based on linear mixed effects ANOVA model with a random effect of subject and a fixed effect of fasting status.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum plasma concentration; LS, least squares; N, number of subjects in the pharmacokinetic analysis set; n, number of data points included in the analysis; PK, pharmacokinetic

Part 2 (MAD)

Following once daily dose administration of AZD7986 at 10 mg for 21 days, or at 25 mg and 40 mg for 28 days, the accumulation ratios for C_{max} and AUC were 1.8 and 2.3, respectively, for 10 mg, 1.7 and 2.3, respectively, for 25 mg, and 1.9 and 2.5, respectively, for 40 mg, at steady-state compared to single dose.

Neutrophil elastase activity was evaluated as a PD biomarker. The percent changes in relative NE activity appear dose dependent over the treatment period (i.e., 21 or 28 days). Relative NE activity appears to return to baseline levels after cessation of dosing.

Figure 23. Geometric Mean Plasma Concentrations (nmol/L) of AZD7986 vs. Time Following a Single AZD7986 Dose on Day 1 and Daily Dosing on Days 21 or 28 in Healthy Subjects Under Fasted Conditions



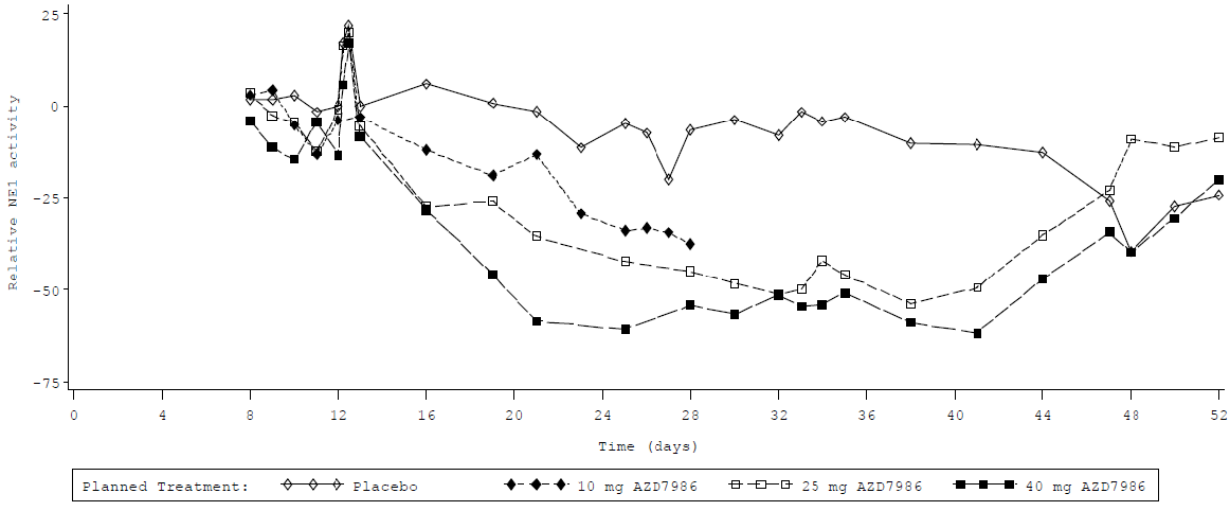
Source: Adapted from Figure 11-8 of Study D6190C00001 CSR
Abbreviation: h, hour

Table 58. Summary of AZD7986 PK Parameters Following a Single AZD7986 Dose on Day 1 and Daily Dosing on Days 21 or 28 in Healthy Subjects Under Fasted Conditions

Parameter (Unit)		Day 1			Day 21	Day 28	
		AZD7986 10 mg (n = 6)	AZD7986 25 mg (n = 8)	AZD7986 40 mg (n = 10)	AZD7986 10 mg (n = 6)	AZD7986 25 mg (n = 7)	AZD7986 40 mg (n = 10)
$AUC_{(0\text{-last})}$ (h·nmol/L)	GeoMean	1278	3256	6427	5135	14320	29550
	CV%	(18.9)	(15.9)	(31.0)	49.4	39.5	53.5
AUC_{τ} (h·nmol/L)	GeoMean	1277	3259	6433	2834	7499	15660
	CV%	(18.9)	(15.9)	(31.0)	(35.1)	(27.4)	(43.3)
AUC (h·nmol/L)	GeoMean	1778[$]	4957[$]	9866[$]	5565	16660	33220
	CV%	(21.3)	(19.5)	(35.8)	54.3	44.2	58.5
C_{max} (nmol/L)	GeoMean	138.6	350.9	672.0	246.3	598.1	1235
	CV%	(18.3)	(19.3)	(37.0)	(26.2)	(15.5)	(37.7)
t_{max} (h)	Median	1.51	0.75	0.75	1.50	0.75	1.12
	Min, Max	(0.52, 1.53)	(0.53, 2.00)	(0.52, 1.50)	(0.75, 1.50)	(0.52, 2.00)	(0.53, 1.50)
$t_{1/2\lambda z}$ (h)	ArithMean	12.82[$]	14.85[$]	15.85[$]	25.85	33.78	30.04
	SD	(1.477)	(2.244)	(4.132)	(5.501)	(10.31)	(5.483)
MRT (h)	ArithMean	18.56	21.84	22.64	33.73	40.16	37.46
	SD	(2.245)	(3.067)	(5.844)	(9.663)	(10.58)	(8.157)
CL/F (L/h)	ArithMean	13.61	12.20	10.24	8.786	8.165	6.577
	SD	(2.665)	(2.485)	(4.206)	(2.772)	(2.025)	(2.867)
Vz/F (L)	ArithMean	248.9	256.7	222.7	311.8	393.2	269.6
	SD	(38.94)	(36.11)	(65.93)	(56.96)	(163.1)	(79.13)
Rac $_{AUC(0\text{-}\tau)}$	ArithMean	NA	NA	NA	2.257	2.330	2.476
	SD	NA	NA	NA	(0.4560)	(0.4828)	(0.4521)
Rac $_{Cmax}$	ArithMean	NA	NA	NA	1.799	1.667	1.881
	SD	NA	NA	NA	(0.3084)	(0.2007)	(0.4015)
TCP	ArithMean	NA	NA	NA	1.610	1.535	1.599
	SD	NA	NA	NA	(0.2539)	(0.2479)	(0.2082)

Source: Table 11-8 of Study D6190C00001 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; Rac, reference amounts customarily consumed; SAD, single ascending dose; $t_{1/2}$, half-life; TCP, temporal change parameter, estimated as AUC(0-τ) Day 21/AUC Day 1, if extrapolated part was less than 20%; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Figure 24. Mean Relative Neutrophil Elastase Activity (NE1) in Healthy Subjects (Linear Scale), Study D6190C00001



Source: Figure 11-17 of Study D6190C00001 CSR
The relative NE activity is a measure of the percentage change in NE activity.
Abbreviations: NE, unstimulated NE; NE1, stimulated

14.2.2. Study D6190C00003

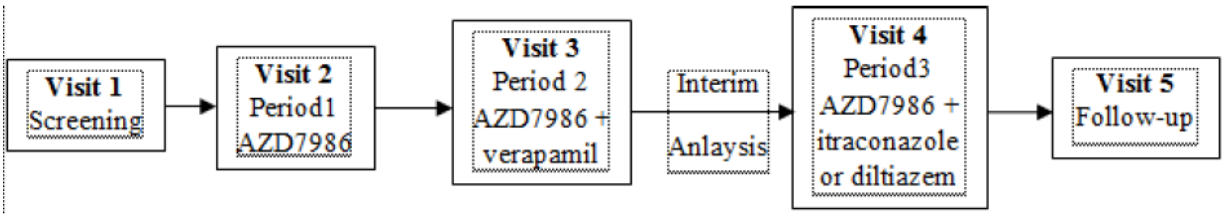
Title

An open-label, non-randomized, fixed sequence study assessing the pharmacokinetics of AZD7986 when administered alone and with multiple doses of verapamil and itraconazole or diltiazem in healthy subjects

Study Design

This study was an open-label, non-randomized, single-center, fixed sequence, 3-period study in healthy subjects (n=15) to evaluate the impact of CYP3A4 inhibitors on AZD7986 pharmacokinetics. In Period 1, a single dose of 25 mg AZD7986 was administered on Day 1 (1 hour before food) and then followed by at least a 7-day washout period. In Period 2, verapamil (240 mg, extended-release formulation) (a moderate CYP3A4 inhibitor) was administered daily (1 hour before food) on Days 1 to 10 plus administration of a single dose of AZD7986 (25 mg) on Day 5 (1 hour before food), and then followed by at least a 14-day washout period. An interim analysis was performed and determined to administer itraconazole (a strong CYP3A4 inhibitor) instead of diltiazem (an alternative moderate CYP3A4 inhibitor) in Period 3. Itraconazole (200 mg; oral solution 10 mg/mL) was administered twice on Day 1 and then daily on Days 2 to 11 (1 hour before food) plus administration of AZD7986 (25 mg) as a single dose on Day 6 (1 hour before food).

Figure 25. Study Design, Study D6190C00003



Source: Figure 9-1 of Study D6190C00003 CSR

Study Formulation

Oral solution (15 mg/mL).

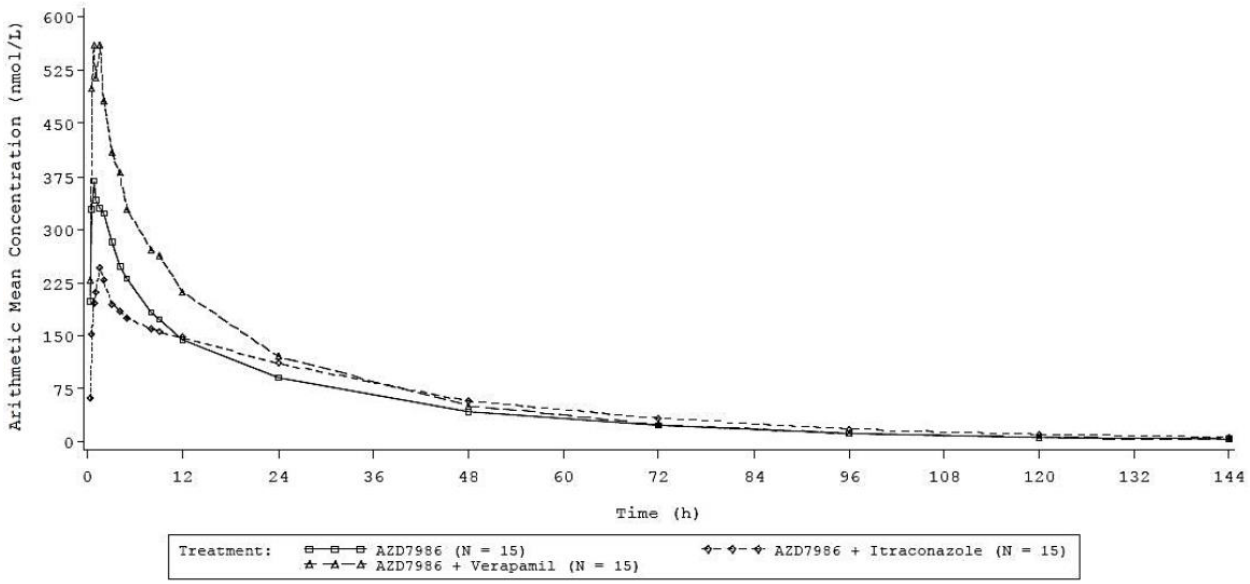
Sampling

- Period 1: Predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 9, 12, 24, 48, 72, 96, 120 and 144 hours postdose
- Period 2: on Day 5, predose and at 0.25, 0.5, 0.75, 1, 1.5, 2,3, 4, 5, 8, 9, 12, 24, 48, 72, 96, 120 and 144 hours postdose
- Period 3: on Day 6, predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 9, 12, 24, 48, 72, 96, 120 and 144 hours postdose

Results

When co-administered with verapamil (a moderate CYP3A4 inhibitor), AZD7986 C_{max} and AUC increased by 53% and 34%, respectively, compared to when AZD7986 was administered alone. When co-administered with itraconazole (a strong CYP3A4 inhibitor), AZD7986 C_{max} decreased by 39% and AUC increased by 14% (although the AUC GMR 90% CI remained within 80 to 125%), compared to when AZD7986 was administered alone.

Figure 26. Arithmetic Mean PK Profiles of AZD7986 When Administered Alone and Coadministered With Itraconazole or Verapamil



Source: Figure 11-2 of Study D6190C00003 CSR
Abbreviations: h, hour; PK, pharmacokinetic

Table 59. Summary of AZD7986 PK Parameters When Administered Alone and Coadministered With Itraconazole or Verapamil

Parameter (Unit)		AZD7986 Day 1 (n = 15)	AZD7986 + verapamil (n = 15)	AZD7986 + itraconazole (n = 15)
AUC (h·nmol/L)	Geometric Mean	6697	8857	7615
	CV%	44.8	43.3	35.1
AUC_{last} (h·nmol/L)	Geometric Mean	6545	8739	7361
	CV%	44.8	43.5	34.4
C_{max} (nmol/L)	Geometric Mean	385.8	591.9	234.1
	CV%	27.4	27.1	39.0
t_{max} (h)	Median	0.75	1.50	1.50
	Min, Max	0.48, 3.00	0.73, 1.52	0.75, 2.00
$t_{1/2\lambda z}$ (h)	Arithmetic Mean	23.35	20.36	27.89
	SD	5.731	4.812	5.407
CL/F (L/h)	Arithmetic Mean	9.807	7.359	8.308
	SD	5.267	3.765	3.452
Vz/F (L)	Arithmetic Mean	297.1	194.6	317.8
	SD	83.48	41.68	89.06

Source: Table 11-1 of Study D6190C00003 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; n, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 60. Summary of AZD7986 PK Comparison When Administered Alone and Co-administered With Itraconazole or Verapamil

Pharmacokinetic parameter (Unit)	Treatment	n	Geometric LS Mean	95% CI	Pairwise Comparison		
					Pair	Ratio	90% CI
C_{max} (nmol/L)	AZD7986	15	385.8	[327.8, 454.1]			
	AZD7986 + verapamil	15	591.9	[502.9, 696.6]	AZD7986 + verapamil / AZD7986	153.40	[136.16, 172.83]
	AZD7986 + itraconazole	15	234.1	[198.9, 275.5]	AZD7986 + itraconazole / AZD7986	60.66	[53.84, 68.34]
AUC_{last} (h*nmol/L)	AZD7986	15	6545	[5311, 8066]			
	AZD7986 + verapamil	15	8739	[7091, 10770]	AZD7986 + verapamil / AZD7986	133.51	[122.70, 145.29]
	AZD7986 + itraconazole	15	7361	[5973, 9071]	AZD7986 + itraconazole / AZD7986	112.45	[103.34, 122.37]
AUC (h*nmol/L)	AZD7986	15	6697	[5431, 8258]			
	AZD7986 + verapamil	15	8857	[7183, 10920]	AZD7986 + verapamil / AZD7986	132.25	[121.78, 143.64]
	AZD7986 + itraconazole	15	7615	[6175, 9390]	AZD7986 + itraconazole / AZD7986	113.70	[104.69, 123.49]

Source: Table 11-2 of Study D6190C00003 CSR
Result based on analysis of variance (ANOVA) of log-transformed PK parameter with treatment as fixed effect and subject as random effect. Geometric mean ratio and CI were back-transformed and presented as percentages. Geometric LS mean and 95% CI were also back-transformed.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; N, number of subjects in all pharmacokinetic analysis set who received treatment; n, all subjects included in the statistical comparison analysis; PK, pharmacokinetic

Cyclodextrins are commonly used pharmaceutical excipients in oral drug products, such as in the oral solution of itraconazole. It has been reported that in DDI studies using itraconazole oral solution, hydroxypropyl-β-cyclodextrin (HP-β-CD) may have excipient–drug interaction with the potential victim drug by forming a pre-systemic complex, which consequently affects the oral absorption of the victim drug and confounds the DDI study.

This study was discussed in a Type B meeting dated December 05, 2022 (under IND 133790). The Agency commented that "In the clinical DDI Study D6190C00003, there was an unexpected 40% decrease on brensocatib C_{max} in the presence of itraconazole (strong CYP3A and P-gp inhibitor) and the interaction effect was lower compared to the effect of verapamil (moderate CYP3A and P-gp inhibitor). The solution formulation of itraconazole used in this study (Sporanox) contains HP-β-CD as an excipient. It has been known that HP-β-CD may have impact on the rate and extent of a victim drug absorption when co-administered with itraconazole solution, which can lead to underestimation of the DDI effect of itraconazole (Chen et al. 2020; Durk et al. 2020). We recommend that you investigate any potential impact of HP-β-CD on the observed DDI between itraconazole and brensocatib." To address the Agency's concern, the Applicant conducted another DDI study (INS1007-109) using clarithromycin as an index inhibitor to evaluate the effect of CYP3A4 inhibition on the pharmacokinetics of brensocatib. Thus, the change in brensocatib exposure following coadministration with itraconazole is not considered representative of the impact of a strong CYP3A4 inhibitor.

14.2.3. Study INS1007-101

Title

A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses and the Open-Label Food Effect of a Single Dose of INS1007 in Healthy Japanese and Caucasian Subjects

Study Design

The study was conducted sequentially in 2 parts.

Part A was a randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of INS1007 in healthy adult Japanese and Caucasian subjects. On Day 1, subjects were administered INS1007 after overnight fasting for at least 10 hours. From Day 4 to Day 30, subjects received INS1007 or placebo once daily after overnight fasting of at least 10 hours.

Part B was an open-label, two-period, and two-sequence crossover study to assess the food effect on INS1007. The fasted and fed administrations were separated by at least 7 days. If under fed conditions, INS1007 was administered, with 240 mL of room temperature water, approximately 30 minutes after the start of the breakfast and within 5 minutes of the subject completing the high-fat and high-calorie breakfast, including 2 eggs, 2 strips of bacon, toast with butter, hashbrown and whole milk (total calorie count was 990 kcal, fat content was 57 g (513 kcal)).

Table 61. Cohorts and Dose Administration in Part A

Dose Cohorts	Japanese Number of Subjects	Caucasian Number of Subjects	Treatment
Cohort 1 (10 mg)	N = 8 Active N = 2 Placebo	N = 8 Active N = 2 Placebo	INS1007 10 mg, or Placebo
Cohort 2 (25 mg)	N = 8 Active N = 2 Placebo	N = 8 Active N = 2 Placebo	INS1007 25 mg, or Placebo
Cohort 3 (40 mg)	N = 8 Active N = 2 Placebo	N = 8 Active N = 2 Placebo	INS1007 40 mg, or Placebo

Source: Table 9-1 of Study INS1007-101 CSR

Table 62. Dose Administration in Part B

Treatment Sequence		Treatment Period 1	Treatment Period 2
1	Japanese, N = 5; Caucasian, N = 5	INS1007 40 mg, Fed	INS1007 40 mg, Fasted
2	Japanese, N = 5; Caucasian, N = 5	INS1007 40 mg, Fasted	INS1007 40 mg, Fed

Source: Table 9-1 of Study INS1007-101 CSR

Study Formulation

INS1007 film-coated tablet (10 mg, 15 mg, 25 mg, by (b) (4) The 40-mg dose was achieved by administering 15 mg and 25-mg tablets together.

Sampling

- Part A: pre-dose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 72-hours postdose on Day 1 and Day 30. Predose on other days.
- Part B: pre-dose on Day 1 and Day 8, and 0.25, 0.5, 1, 1.5, 2, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, and 72-hours postdose in each treatment period.

Results

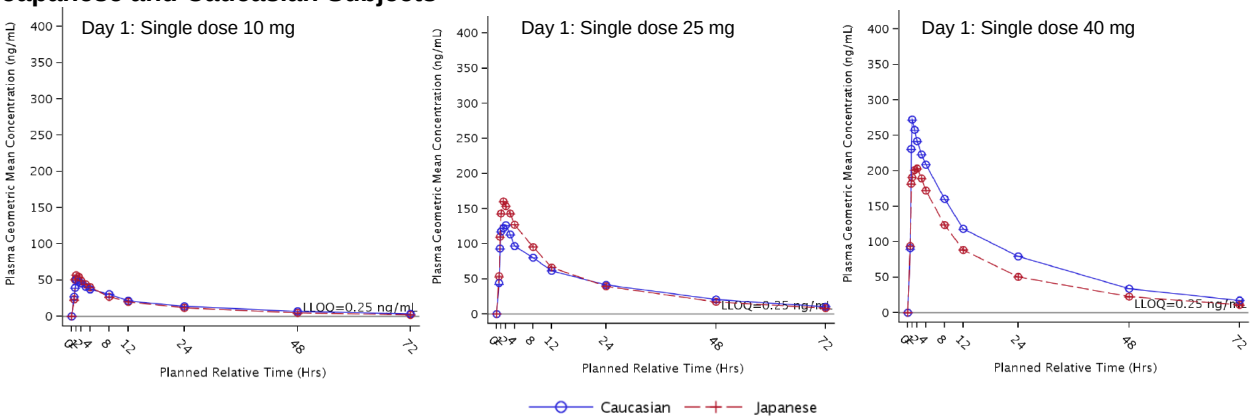
Part A

Following single or multiple dose administration, the median T_{max} of INS1007 ranged from 1 to 1.75 hours and the geometric mean $T_{1/2}$ ranged from 23 to 28 hours in healthy Caucasian subjects, and from 21 to 23 hours in healthy Japanese subjects. Following single or multiple dose administration of 10 mg and 25 mg, INS1007 exposure was generally comparable between Caucasian and Japanese subjects. At the 40-mg dose, INS1007 exposure in Caucasian subjects was higher than in Japanese subjects on both Day 1 and on Day 30. Following once daily dosing

from Day 4 to Day 30, the mean accumulation ratios ranged from 1.8-2.1 folds for AUC and 1.5 to 1.7 folds for C_{max} in Caucasian subjects and ranged from 1.6 to 2.1-fold for AUC and 1.2 to 1.5-fold for C_{max} in Japanese subjects.

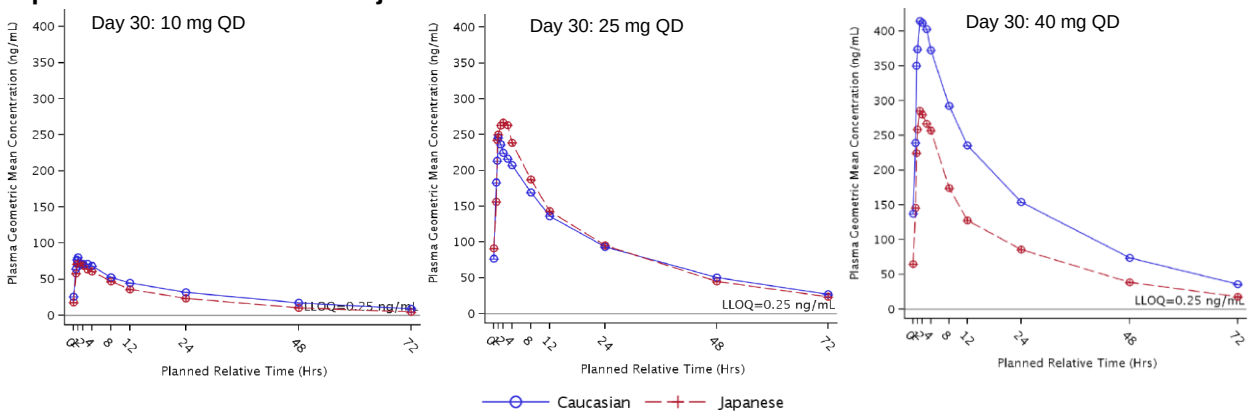
In healthy Caucasian subjects (n=8/dose), following 10 to 40 mg QD dosing, brensocatib steady state C_{max} and AUC_{tau} increased by 5.1 and 5.3 folds, respectively, indicating brensocatib exposure increased more than dose proportionally over the dose range of 10 to 40 mg.

Figure 27. Mean Plasma INS1007 PK Profile Following a Single Dose Administration in Healthy Japanese and Caucasian Subjects



Source: adapted from Figures 11-1, 11-2, 11-3 of Study INS1007-101 CSR
Abbreviation: PK, pharmacokinetic

Figure 28. Mean Plasma INS1007 PK Profile Following Multiple Doses Administration in Healthy Japanese and Caucasian Subjects



Source: adapted from Figures 11-1, 11-2, 11-3 of Study INS1007-101 CSR
Abbreviations: PK, pharmacokinetic; QD, once daily

Table 63. Summary of INS1007 PK Parameters Following Single Oral Dose Administration (10, 25, and 40 mg) in Healthy Japanese and Caucasian Subjects

Parameter (Unit)	Statistic	10 mg		25 mg		40 mg	
		Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian
C_{max} (ng/mL)	n	8	8	9	8	8	8
	GeoMean	63.65	54.01	199.1	150.4	234.6	304.6
	CV% GeoMean	17.6	29	35.8	41.8	32.6	45.3
T_{max} (h)	n	8	8	9	8	8	8
	Median	1.02	1.01	1.50	1.35	1.50	1.27
	Range	0.75 - 2.00	1.00 - 2.00	0.75 - 8.00	0.50 - 3.00	0.77 - 3.02	0.50 - 7.78
$AUC_{0-\tau}$ (h*ng/mL)	n	8	8	9	8	8	8
	GeoMean	598.6	610.1	1942	1686	2534	3350
	CV% GeoMean	33.4	19.7	28.0	21.1	33.5	23.0
AUC_{0-last} (h*ng/mL)	n	8	8	9	8	8	8
	GeoMean	871.4	974.6	2899	2763	3804	5247
	CV% GeoMean	44.0	18.0	33.8	19.7	38.2	15.4
AUC_{0-inf} (h*ng/mL)	n	8	8	9	8	8	8
	GeoMean	935.9	1118	3194	3155	4228	5888
	CV% GeoMean	48.0	19.1	38.4	19.9	44.3	12.4
$AUC_{\%extrap}$ (%)	n	8	8	9	8	8	8
	GeoMean	5.818	10.56	8.156	11.68	8.525	9.230
	CV% GeoMean	70.8	69.1	57.5	33.7	72.6	63.5
λ_z (1/h)	n	8	8	9	8	8	8
	GeoMean	0.03764	0.02831	0.03246	0.02857	0.03093	0.03221
	CV% GeoMean	21.7	33.1	20.7	15.3	29.7	25.1
$t_{½}$ (h)	n	8	8	9	8	8	8
	GeoMean	18.42	24.49	21.35	24.26	22.41	21.52
	CV% GeoMean	21.7	33.1	20.7	15.3	29.7	25.1

Source: Table 11-7 of Study INS1007-101 CSR
Abbreviations: AUC, area under the concentration-time curve; CV%, coefficient of variation; C_{max}, maximum plasma concentration; n, number of subjects; GeoMean, geometric mean; n, number of subjects in the specific category; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time to maximum concentration

Table 64. Summary of INS1007 PK Parameters Following Multiple Oral Dose Administration (10, 25, and 40 mg) in Japanese and Caucasian Subjects

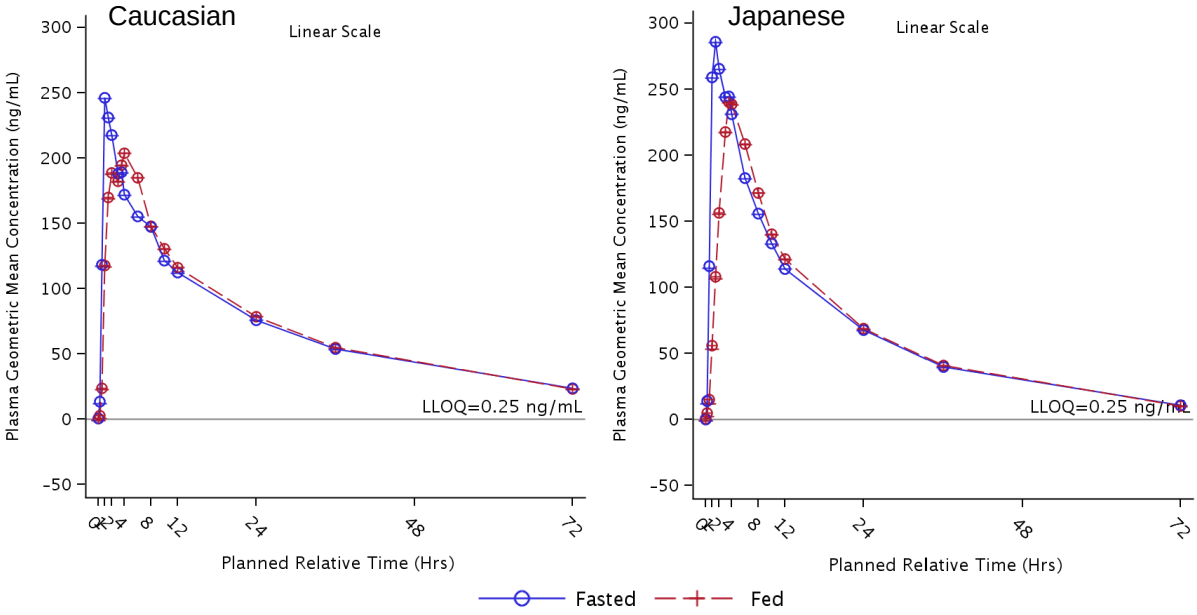
Parameter (Unit)	Statistic	10 mg		25 mg		40 mg	
		Japanese	Caucasian	Japanese	Caucasian	Japanese	Caucasian
$C_{max,ss}$ (ng/mL)	n	8	8	8	8	7	8
	GeoMean	78.52	88.16	286.0	253.6	321.9	447.9
	CV% GeoMean	25.0	18.8	35.4	34.3	29.8	33.0
$T_{max,ss}$ (h)	n	8	8	8	8	7	8
	Median	1.26	1.02	1.75	1.02	1.03	1.49
	Range	0.50 - 2.00	0.77 - 3.00	0.78 - 3.00	0.77 - 1.50	0.77 - 4.00	0.78 - 3.00
C_{trough} (ng/mL)	n	8	8	8	7	7	8
	GeoMean	12.16	27.84	74.46	76	22.47	26.64
	CV% GeoMean	128.8	60.3	81.4	47.3	2527.0	1658.6
$AUC_{0-\tau,ss}$ (h*ng/mL)	n	8	8	8	8	7	8
	GeoMean	989.3	1173	3888	3580	3725	6178
	CV% GeoMean	39.3	15.7	41.6	46.5	41.5	34.0
AUC_{0-last} (h*ng/mL)	n	8	8	8	8	7	8
	GeoMean	1569	2070	6266	6123	5862	10040
	CV% GeoMean	51.6	19.3	49.7	50.8	47.0	37.7
AUC_{0-inf} (h*ng/mL)	n	8	8	8	8	7	8
	GeoMean	1762	2476	7082	7342	6470	11450
	CV% GeoMean	58.2	24.4	53.9	54.9	49.3	41.5
$t_{½,ss}$ (h)	n	8	8	8	8	7	8
	GeoMean	22.06	27.59	23.13	27.24	21.69	22.85
	CV% GeoMean	22.1	21.2	13.0	33.9	15.9	27.4
$\lambda_{z,ss}$ (1/h)	n	8	8	8	8	7	8
	GeoMean	0.03143	0.02513	0.02997	0.02544	0.03195	0.03033
	CV% GeoMean	22.1	21.2	13.0	33.9	15.9	27.4
$CL/F_{,ss}$ (L/h)	n	8	8	8	8	7	8
	GeoMean	10110	8526	6431	6984	10740	6474
	CV% GeoMean	39.3	15.7	41.6	46.5	41.5	34.0
$V_z/F_{,ss}$ (L)	n	8	8	8	8	7	8
	GeoMean	321600	339300	214600	274500	336000	213500
	CV% GeoMean	23.9	24.6	30.2	55.5	39.0	39.6
$C_{av,ss}$ (ng/mL)	n	8	8	8	8	7	8
	GeoMean	41.22	48.87	162.0	149.2	155.2	257.4
	CV% GeoMean	39.3	15.7	41.6	46.5	41.5	34.0
$C_{min,ss}$ (ng/mL)	n	8	8	8	8	7	8
	GeoMean	17.94	25.77	88.66	76.36	65.23	136.6
	CV% GeoMean	49.5	23.7	51.9	85.9	67.8	49.3
$AUC_{\%extrap}$ (%)	n	8	8	8	8	7	8
	GeoMean	9.508	15.15	11.00	14.34	8.709	10.33
	CV% GeoMean	61.2	39.5	33.0	55.4	49.1	68.5
$RacAUC_{0-\tau}$	n	8	8	8	8	7	8
	GeoMean	1.653	1.922	2.079	2.124	1.580	1.844
	CV% GeoMean	14.8	13.4	14.2	27.6	18.9	38.3
$RacC_{max}$	CV%	8	8	8	8	7	8
	GeoMean	1.234	1.632	1.481	1.685	1.472	1.471
	CV% GeoMean	29.3	14.8	20.9	29.3	24.2	53.9

Source: Table 11-8 of Study INS1007-101 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, trough concentration; CV%, coefficient of variation; GeoMean, geometric mean; n, number of subjects in the specific category; PK, pharmacokinetic; Rac, reference amounts customarily consumed; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Part B

Following 40 mg single dose administration, the T_{max} was delayed from 1.3 hours (fasted) to 3.0 hours (fed) in Japanese subjects, and to 2.0 hours (fed) in Caucasian subjects. In general, INS1007 exposure (C_{max} and AUC) was comparable under fed conditions compared to fasted conditions in both Japanese and Caucasian subjects. Although, an 18% lower C_{max} was observed in the fed state for Japanese subjects.

Figure 29. Mean Plasma INS1007 PK Profiles After 40 mg Single Dose Administration Under Fasted and Fed Conditions in Healthy Caucasian and Japanese Subjects



Source: Adapted from Figures 11-6 and 11-7 of Study INS1007-101 CSR
Abbreviations: LLOQ, lower limit of quantification; PK, pharmacokinetic

Table 65. Summary of INS1007 PK Parameters After 40 mg Single Dose Administration Under Fasted and Fed Conditions in Healthy Caucasian and Japanese Subjects

Parameter (Unit)	Statistic	Fasted		Fed	
		Japanese	Caucasian	Japanese	Caucasian
C_{max} (ng/mL)	n	10	10	9	10
	GeoMean	338.4	268.9	288.9	272.2
	CV% GeoMean	30.3	61.4	26.3	53.0
T_{max} (h)	n	10	10	9	10
	Median	1.27	1.25	3.00	2.00
	Range	0.48-3.50	0.52-8.00	0.48-6.00	1.00-6.00
$AUC_{0\text{-last}}$ (h*ng/mL)	n	10	10	9	10
	GeoMean	4820	5147	4751	5214
	CV% GeoMean	29.1	40.8	33.3	35.4
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	10	10	9	10
	GeoMean	5183	6201	5122	6178
	CV% GeoMean	33.9	44.0	39.8	36.1
$t_{½}$ (h)	n	10	10	9	10
	GeoMean	18.67	28.03	18.41	26.95
	CV% GeoMean	26.5	25.2	32.3	21.1
λ_z (1/h)	n	10	10	9	10
	GeoMean	0.03712	0.02473	0.03766	0.02572
	CV% GeoMean	26.5	25.2	32.3	21.1
CL/F (mL/h)	n	10	10	9	10
	GeoMean	7718	6450	7809	6475
	CV% GeoMean	33.9	44.0	39.8	36.1
V_z/F (mL)	n	10	10	9	10
	GeoMean	207900	260800	207400	251700
	CV% GeoMean	19.1	38.8	19.1	35.4
$AUC_{\%extrap}$ (%)	n	10	10	9	10
	GeoMean	5.578	15.32	5.449	14.56
	CV% GeoMean	76.8	45.4	81.5	39.9

Source: Table 11-11 of Study INS1007-101 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV%, coefficient of variation; GeoMean, geometric mean; n, number of subjects in the specific category; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 66. Statistical Analysis of Food Effect in Japanese and Caucasian Subjects

Descent/ Number of Subjects	Parameter (Unit)	LS-mean		Geometric Mean Ratio (%)	90% Confidence Interval
		INS1007 40 mg Fed	INS1007 40 mg Fasted		
Caucasian (N=10)	C_{max} (ng/mL)	272.20	268.86	101.24	(81.41, 125.91)
	$AUC_{0\text{-last}}$ (ng*hr/mL)	5214.17	5146.58	101.31	(96.80, 106.04)
	$AUC_{0\text{-inf}}$ (ng*hr/mL)	6177.69	6201.24	99.62	(94.60, 104.90)
Japanese (N=9)	C_{max} (ng/mL)	292.99	355.80	82.35	(67.86, 99.93)
	$AUC_{0\text{-las)}}$ (ng*hr/mL)	4840.23	4918.93	98.40	(94.43, 102.53)
	$AUC_{0\text{-inf}}$ (ng*hr/mL)	5232.03	5273.96	99.21	(95.71, 102.83)

Source: Table 11-12 of Study INS1007-101 CSR
Test: INS1007 40 mg under fed conditions; Reference: INS1007 40 mg under fasted conditions
Food effect was analyzed using analysis of variance with sequence, treatment group and period as fixed effects and subject (sequence) as random effect, after logarithmic transformation of the data.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; LS, least squares; N, number of subjects exposed to each treatment who were included in the mixed model

14.2.4. Study INS1007-102

Title

A Phase 1, Open-Label, Single-Dose Parallel-Group Study of Brensocatib Following a Single Oral Administration in Subjects With or Without Renal Impairment

Study Design

This was a phase 1, multicenter, open-label, single-dose study designed to assess the effect of impaired renal function on the pharmacokinetics, safety, and tolerability of brensocatib. A total of up to 30 subjects were planned (6 subjects in each renal impairment group and 10 healthy subjects with normal renal function). Subjects received a single oral dose of brensocatib 25 mg on the morning of Day 1 following an overnight fast of at least 8 hours.

Table 67. Cohorts, Study INS1007-102

Cohort	Renal Function	eGFR (mL/min/1.73m^2)	No. of Subjects
1	Mild impairment	60 to <90	6
2	Moderate impairment	30 to <60	6
3	Severe impairment	15 to <30	6
4	Normal (control)	≥90	Up to 12

Source: Page 20 of Study INS1007-102 CSR
Abbreviation: eGFR, epidermal growth factor receptor

Study Formulation

25 mg, (b) (4) film coated tablets (Lot# CFXHF).

Sampling

Blood samples were collected predose and at 0.5, 1, 2, 3, 4, 8, 12, 24, 30, 48, 72 hours, and Day 7, Day 10, and Day 14 after the dose was administered.

Results

Following a single oral administration of 25 mg, brensocatib C_{max} and AUC were comparable in subjects with mild renal impairment compared to subjects with normal renal function. Brensocatib C_{max} and AUC increased by 10% and 27%, respectively, in subjects with moderate renal impairment, but decreased by 17% and 28%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function. The observed exposure changes in subjects with moderate renal impairment and severe renal impairment are not considered clinically relevant. In addition, there was no change in brensocatib half-life in subjects with renal impairment as compared to subjects with normal renal function.

Table 68. Mean (CV) Plasma PK Parameters of Brensocatib by Renal Function Group

	Renal Function Group			
Parameter (unit)	Mild (N=6)	Moderate (N=6)	Severe (N=6)	Normal (N=10)
C_{max} (ng/mL)	183 (43.7)	187 (26.7)	141 (20.3)	168 (24.6)
T_{max} (h)	1.00 (0.50-2.00)	1.00 (1.00-2.00)	1.00 (0.50-3.00)	1.00 (1.00-3.00)
AUC_t (ng•h/mL)	3590 (31.8)	4450 (31.0)	2750 (35.9)	3480 (20.7)
AUC_{inf} (ng•h/mL)	3610 (31.7)	4490 (31.2)	2780 (35.7)	3510 (20.6)
$t_{1/2}$ (h)	37.0 (15.3)	42.8 (21.7)	36.3 (22.9)	39.1 (17.8)
CL/F (L/h)	7.72 (39.9)	6.09 (33.0)	9.97 (33.8)	7.43 (22.6)
V_d/F (L)	397 (29.8)	359 (21.2)	492 (17.0)	411 (19.9)

Abbreviations: AUC_t, area under the plasma concentration curve versus time from time 0 to the last quantifiable measurement; AUC_{inf}, area under the plasma concentration versus time from time 0 extrapolated to infinity; CL/F, total oral clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; h, hours; $t_{1/2}$, elimination half-life; T_{max}, time to reach maximum observed plasma concentration; V_d/F, apparent volume of distribution.

Note: For T_{max} median (minimum, maximum) values are presented, and for all other parameters arithmetic mean (arithmetic CV) results are presented.

Source: Table 11-1 of Study INS1007-102 CSR

Table 69. Statistical Analysis of Plasma PK Parameters of Brensocatib

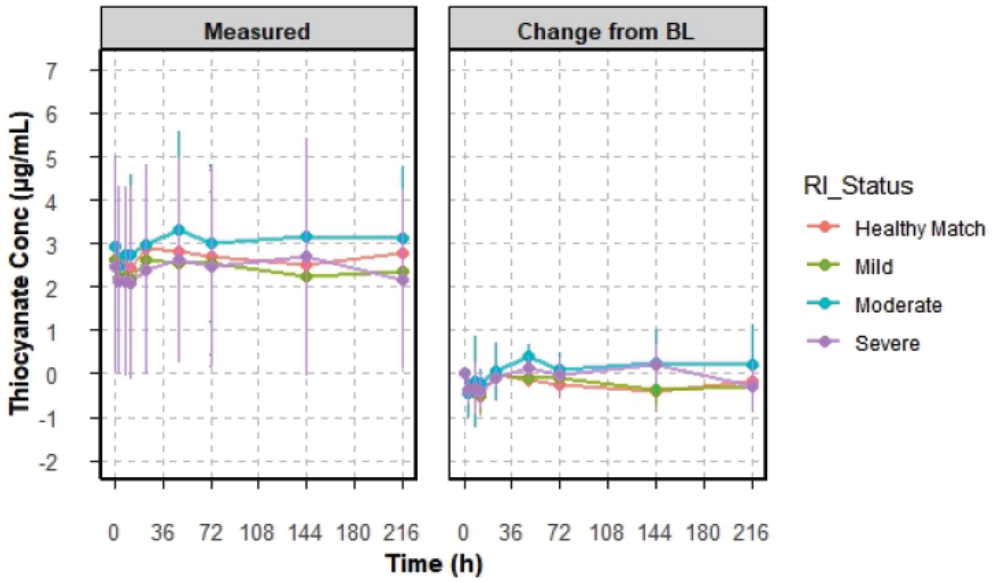
Parameter (units)	Renal Function Group	n	Geometric LS Means	Ratio of Geometric LS Means (Impaired / Normal)	90% CI of the Ratio of Geometric LS Means
C_{max} (ng/mL)	Mild	6	168.8	1.033	(0.755, 1.415)
	Normal	10	163.4		
	Moderate Impairment	6	182.7	1.096	(0.806, 1.490)
	Normal (Matched to Moderate)	6	166.8		
	Severe Impairment	6	139.0	0.831	(0.685, 1.008)
	Normal (Matched to Severe)	6	167.2		
AUC_t (ng•h/mL)	Mild	6	3415.8	1.002	(0.779, 1.290)
	Normal	10	3407.9		
	Moderate Impairment	6	4261.6	1.273	(0.936, 1.730)
	Normal (Matched to Moderate)	6	3348.7		
	Severe Impairment	6	2612.0	0.723	(0.541, 0.967)
	Normal (Matched to Severe)	6	3610.4		
AUC_{inf} (ng•h/mL)	Mild	6	3433.7	0.999	(0.776, 1.285)
	Normal	10	3437.9		
	Moderate Impairment	6	4296.9	1.273	(0.935, 1.731)
	Normal (Matched to Moderate)	6	3376.2		
	Severe Impairment	6	2636.5	0.724	(0.543, 0.966)
	Normal (Matched to Severe)	6	3641.3		
CL/F (L/h)	Mild	6	7.3	1.001	(0.778, 1.288)
	Normal	10	7.3		
	Moderate Impairment	6	5.8	0.786	(0.578, 1.069)
	Normal (Matched to Moderate)	6	7.4		
	Severe Impairment	6	9.5	1.381	(1.035, 1.842)
	Normal (Matched to Severe)	6	6.9		
V_d/F (L)	Mild	6	383.9	0.950	(0.768, 1.176)
	Normal	10	404.0		
	Moderate Impairment	6	352.0	0.897	(0.719, 1.119)
	Normal (Matched to Moderate)	6	392.3		
	Severe Impairment	6	485.8	1.259	(1.023, 1.550)
	Normal (Matched to Severe)	6	385.8		

Source: Table 11-2 of Study INS1007-102 CSR
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; LS, least squares; n, number of subjects; V_d/F, volume of distribution/bioavailability

Metabolite Thiocyanate PK Results (Report VV-NC-000802)

A total of 252 plasma samples were analyzed, where 90 samples were from the normal-matched group (n=10 subjects) and 162 samples were from the renal impairment groups (n=18 subjects). The mean baseline-corrected concentrations for all groups fluctuated around zero (-0.261 to 0.0169µg/mL), with no apparent trend for the change in thiocyanate concentrations with severity of renal impairment. The data indicate little change in thiocyanate concentrations following administration of a single dose of brensocatib.

Figure 30. Mean (± SD) Plasma Concentration Profiles of Thiocyanate Over Time in Subjects With Renal Impairment and Healthy Subjects Following a Single Oral Administration of Brensocatib at 25 mg (Study INS1007-102)



Source: Figure 1 of Report VV-NC-000802
Abbreviations: BL, baseline; h, hour; RI, renal impairment

Table 70. Thiocyanate Plasma Concentrations in Renally Impaired Subjects and Normal Subjects, Study INS1007-102

	Mild	Moderate	Severe	NM
N of Sample	54	54	54	90
N of Subject	6	6	6	10
Measured Thiocyanate Concentrations (µg/mL)				
Mean (SD)	2.40 (1.83)	2.93 (1.68)	2.36 (2.16)	2.67 (1.56)
median	1.86	2.26	1.46	2.52
Range	0.285-6.32	0.997-7.35	0.274-7.20	0.764 – 7.99
Baseline-corrected *Thiocyanate Concentrations (µg/mL)*				
Mean (SD)	-0.243 (0.332)	0.0169 (0.637)	-0.130 (0.425)	-0.261 (0.407)
median	-0.118	0.0384	-0.0550	-0.190
Range	-1.14 – 0.373	-2.19 – 1.61	-1.37 – 1.06	-1.63 – 1.03

Source: Table 1 of Report VV-NC-000802
Abbreviations: N, number; NM, normal subjects

14.2.5. Study INS1007-103

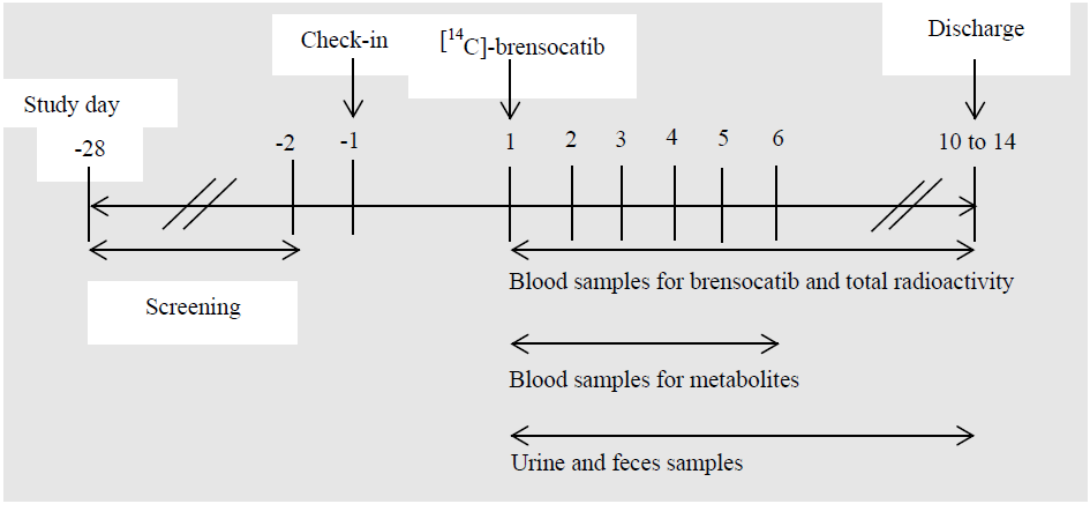
Title

A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [^{14}C]-Brensocatib Following a Single Oral Administration in Healthy Male Subjects

Study Design

This was a phase 1, open-label, nonrandomized, single-dose, mass balance, PK, and metabolite identification study in healthy male subjects (n=7). On the morning of Day 1, subjects received a single oral dose of 40 mg of [^{14}C]-brensocatib containing approximately 100µCi radioactivity in the fasted state.

Figure 31. Study Design (INS1007-103)



Source: Figure 1 of Study INS1007-103 CSR

Study Formulation

Each unit dose contained a total of 40 mg brensocatib containing approximately 100µCi of [^{14}C]-brensocatib

Sampling

- Blood sampling for brensocatib concentration and total radioactivity: Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192 hours postdose, and discharge visit (Days 10 to 14) or early termination
- Blood sampling for metabolite profiling and identification: 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, and 120 hours postdose,

- Urine collection: Predose (−12 to 0 hours), 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, and 192 to 216 hours postdose, and discharge visit (Days 10 to 14) or early termination
- Feces collection: Predose (check-in to 0 hours), 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, and 192 to 216 hours postdose, and discharge visit (Days 10 to 14) or early termination

Results

Recovery of Radioactivity in Urine and Feces

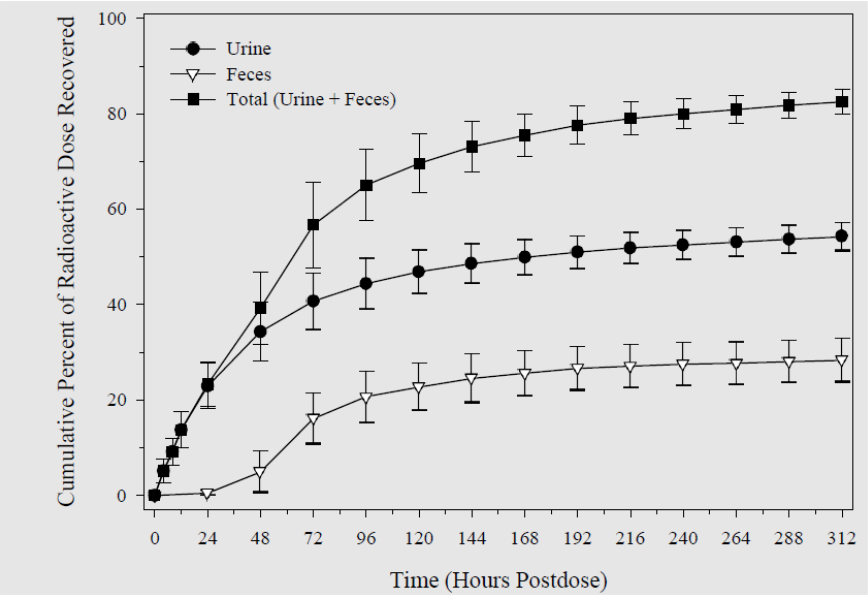
Excreta were collected continuously up to 312 hours postdose for all subjects. Radioactivity was quantifiable for all subjects through the last collection interval (288 to 312 hours postdose) in urine and feces. The overall mean recovery of radioactivity in urine and feces samples was 82.5%, including 54.2% of the dose recovered in urine and 28.3% of the dose recovered in feces. The majority of the recovered radioactivity was excreted in the first 72 hours postdose, with a mean of 56.7% recovered overall in that interval.

Table 71. Summary of the Recovery of Total Radioactivity in Urine, Feces, and Overall Within 312 Hours Following a Single Oral Administration of 40 mg (100µCi) [14C]-Brensocatib

	0 to 312 Hours Postdose
	Cumulative Amount (%)
Analyte (Matrix)	[Mean (range)]
Total Radioactivity (Urine)	54.2 (51.6-59.3)
Total Radioactivity (Feces)	28.3 (23.3-34.5)
Total Radioactivity (Overall)	82.5 (80.0-86.3)

Source: Table 5 of Study INS1007-103 CSR

Figure 32. Mean (±SD) Cumulative Percent Recovery of Total Radioactivity in Excreta Following a Single Oral Administration of 40 mg (100µCi) [14C]-Brensocatib

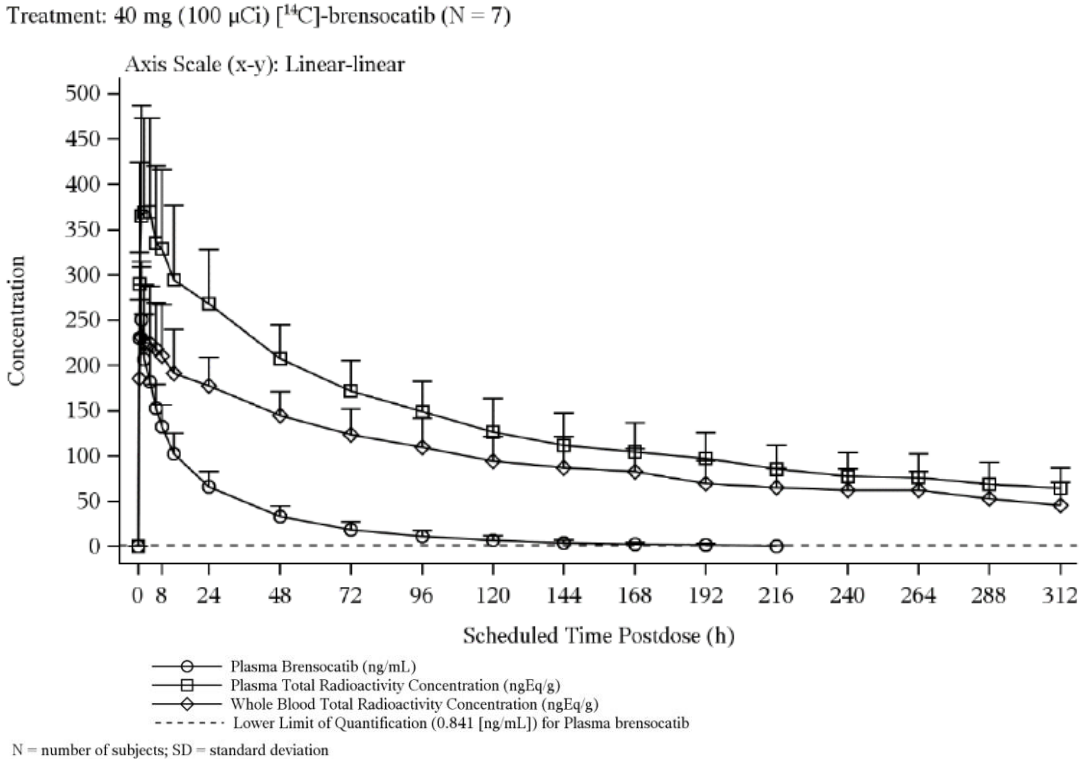


Source: Figure 2 of Study INS1007-103 CSR

Brensocatib Pharmacokinetics in Plasma and Total Radioactivity in Plasma and Whole Blood

Following administration of a single oral dose of 40 mg brensocatib containing ~100µCi of [^{14}C]-brensocatib, the arithmetic mean $T_{1/2}$ of brensocatib was 28.6 hours (range: 18.9 to 38.2 hours). The arithmetic mean whole blood/plasma ratio for total radioactivity was 0.716 based on AUC_{last}.

Figure 33. Arithmetic Mean (+SD) Concentration Profiles for Brensocatib in Plasma and Total Radioactivity in Plasma and Whole Blood Up To 312 Hours Postdose



N = number of subjects; SD = standard deviation
Source: Adapted from Figure 3 of Study INS1007-103 CSR

Table 72. Summary of the PK Parameters for Brensocatib in Plasma and Total Radioactivity in Plasma and Whole Blood

Parameter	Plasma Brensocatib (N = 7)	Plasma Total Radioactivity (N = 7)	Whole Blood Total Radioactivity (N = 7)
AUC_{tlast} (h*ng/mL)[a]	5410 (29.3) [7]	41900 (20.2) [7]	30100 (23.7) [7]
AUC_{∞} (h*ng/mL)[a]	5460 (29.4) [7]	NC (NC) [2]	NC (NC) [1]
C_{max} (ng/mL)[a]	259 (27.3) [7]	384 (29.0) [7]	238 (29.5) [7]
t_{max} (h)	1.00 (0.500-1.00) [7]	2.00 (1.00-6.03) [7]	1.00 (1.00-6.03) [7]
$t_{1/2}$ (h)	28.6 (26.9) [7]	164 (19.7) [7]	177 (16.5) [7]
CL/F (L/h)	8.24 (25.6) [7]	---	---
V_z/F (L)	323 (17.4) [7]	---	---
AUC_{tlast} plasma brensocatib / total radioactivity ratio	0.128 (14.4) [7]	---	---
AUC_{tlast} whole blood / plasma total radioactivity ratio	---	---	0.716 (5.1) [7]
AUC_{∞} plasma brensocatib / total radioactivity ratio	NC (NC) [1]	---	---
AUC_{∞} whole blood / plasma total radioactivity ratio	---	---	NC (NC) [1]
CL_R (L/h)	1.53 (18.3) [7]	---	---

[a] Units for total radioactivity AUCs and C_{max} are (h*ngEq/mL) and (ngEq/mL) respectively.
AUC_{∞} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{tlast} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F = total clearance; CL_R = renal clearance; C_{max} = maximum observed concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; NC = not calculated;
$t_{1/2}$ = apparent terminal elimination half life; t_{max} = time of the maximum observed concentration;
V_z/F = volume of distribution during the terminal phase.
Arithmetic mean (CV %) [n] statistics presented; for t_{max}, median (min-max) [n] statistics presented,
Source: Table 6 of Study INS1007-103 CSR

Brensocatib PK in Urine

When collected for up to 312 hours post-dose, the arithmetic mean fraction of the dose excreted as unchanged brensocatib in urine was approximately 19.3%.

Table 73. Summary of Brensocatib PK Parameters in Urine

	Urine Brensocatib 0-312 hours postdose (N = 7)
Cum A_{eu} (mg)	8.16 (25.2) [7]
Cum f_{eu} (%)	19.3 (24.9) [7]

Cum A_{eu} = cumulative amount of the dose administered recovered in urine; Cum f_{eu} = cumulative percentage of the dose administered recovered in urine; CV = coefficient of variation; n = number of subjects with valid observations; N = number of subjects.
Arithmetic mean (CV %) [n] statistics presented.
Source: Table 7 of Study INS1007-103 CSR

Metabolite Profiling and Identification

Brensocatib underwent moderate metabolism in human subjects, primarily by oxidation, hydrolysis, oxidative dealkylation, sulfuration, and carbamoyl glucuronidation. A total of 27 quantifiable metabolites were detected in plasma, urine, and feces, among which the structures of 9 metabolites were identified.

Based on AUC_{last} in human plasma, unchanged brensocatib accounted for 16.2% of the total radioactivity. Thiocyanate (M8) was identified as a major circulating metabolite, accounting for 51% of the total plasma radioactivity based on AUC_{last}. All other metabolites were minor metabolites with <1% of total AUC_{last}.

Based on pooled urine samples from 0 to 240 hours, unchanged brensocatib was the most abundant component, accounting for 22.8% of the radioactive dose. All other components were

minor (<10% of dose) to trace (<1% of dose) in abundance. Based on the 48 to 96-, 120 to 168-, and 192 to 312-hour pools, brensocatib was the most abundant component in urine, accounting for a total of 6.25% of the radioactive dose. Thiocyanate (M8) was a minor urinary metabolite, accounting for a total of 1.62% of the dose. All other components were minor (<10% of dose) to trace (<1% of dose) in abundance.

In feces, based on the pooled samples from 0 to 216 hours, M17 was the most abundant, accounting for 3.75% of the radioactive dose. Brensocatib, M13, and M33 accounted for 2.41%, 1.26%, and 1.18% of the dose, respectively. All other metabolites were trace in abundance. Based on the 48 to 96-, 120 to 168-, and 192 to 312-hour pools, M17 was the most abundant component in feces, accounting for a total of 2.65% of the radioactive dose. All other components were minor (<10% of dose) to trace (<1% of dose) in abundance.

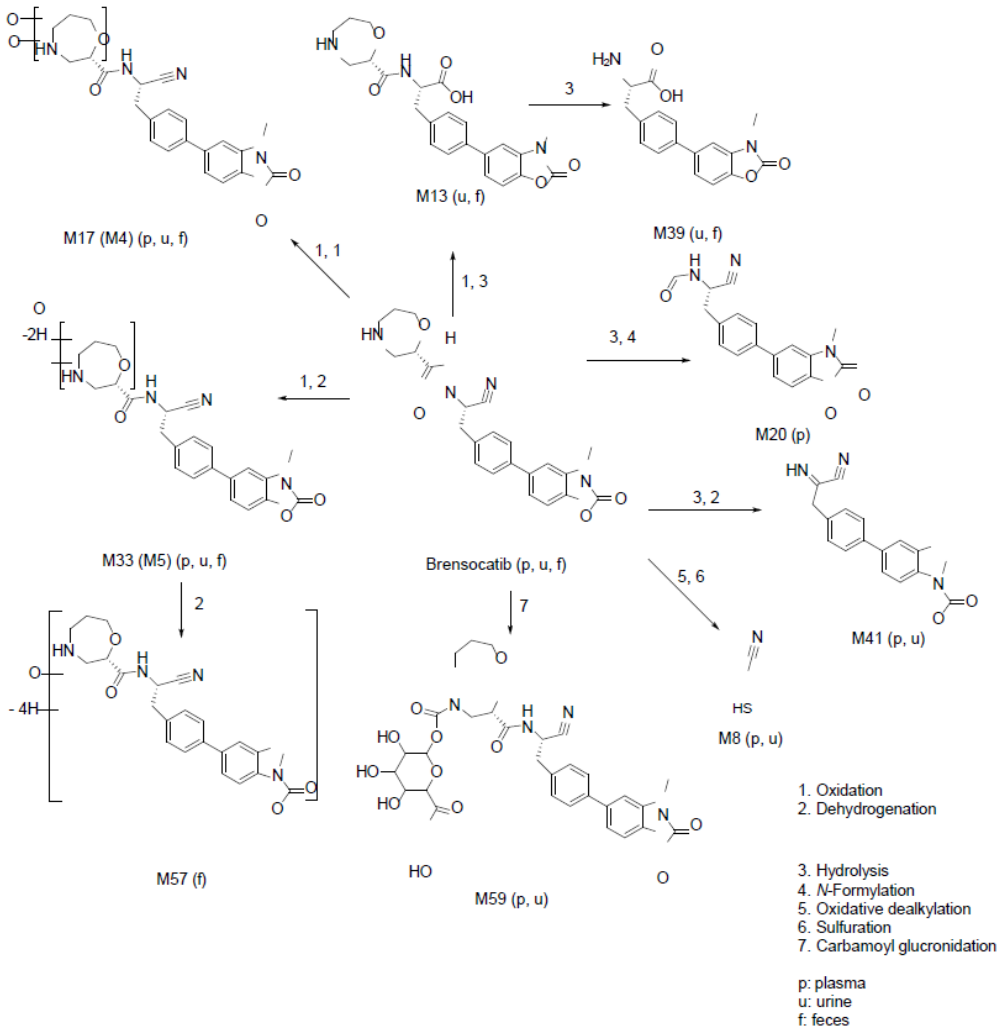
Table 74. Summary of Brensocatib Radiolabeled Components in Plasma, Urine, and Feces

Component Designation	Retention Time (Minutes)	Proposed Identification	Matrix		
			Plasma	Urine	Feces
M8	2.50-2.83/3.00	thiocyanate	X	X	
M38	3.50	Unknown		X	
M39	15.00-15.50	des(oxazepane carbaldehyde) brensocatib-carboxylic acid		X	X
M40	18.00	Unknown			X
M41	18.17	des(oxazepane carbaldehyde)-dehydro-brensocatib	X		
M42	21.67	Unknown			X
M13	22.83-23.33	descyano-brensocatib carboxylic acid		X	X
M43	26.50	Unknown		X	
M44	26.67	Unknown			X
M17 (M4)	27.00-28.33	dioxy-brensocatib	X	X	X
brensocatib	28.33-29.67	brensocatib	X	X	X
M58	29.50	Unknown			X
M45	30.67-30.83	Unknown		X	
M20	31.50	desoxazepane-*N*-formyl-brensocatib	X		
M46	32.17-32.33	Unknown		X	
M47	32.33	Unknown			X
M48	32.67-32.83	Unknown		X	X
M49	33.00-33.17	Unknown			X
M50	33.33-33.50	Unknown			X
M51	33.83	Unknown		X	
M52	33.83-34.00	Unknown			X
M53	34.67	Unknown			X
M54	35.17	Unknown			X
M55	35.50	Unknown			X
M56	35.83	Unknown			X
M59[a]	36.00-37.00	brensocatib carbamoyl glucuronide	X	X	
M59	36.00-36.18	brensocatib carbamoyl glucuronide		X	
M33 (M5)	38.67-39.50	oxy-dehydro-brensocatib	X	X	X
M57	42.00	oxy-didehydro brensocatib			X

Notes: Retention time ranges are from profiling analyses of all matrices.
Component is found in matrix designated with "X".
[a] Source fragment.
Source: Labcorp Early Development Laboratories Inc. Study 8462137.

Source: Table 8 of Study INS1007-103 CSR

Figure 34. Proposed Major Metabolic Pathways of Brensocatib in Humans



Note: Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.

Source: Figure 4 of Study INS1007-103 CSR

Table 75. PK Parameters for Brensocatib and Metabolites in Pooled Plasma Samples After a Single Oral Dose of [14C]-Brensocatib in Male Human Subjects (40 mg)

	Parameter				
Component Designation	C_{max} (ng eq/g)	t_{max} (h)	AUC_{tlast} (ng eq h/g)	AUC_{∞} (ng eq h/g)	$t_{1/2}$ (h)
brensocatib	246	0.5	6781	7174	17.7
M8	107	24	21384	NR[a]	NR[b]
M41	40.1	4	209	NC	NC
M20	19.2	8	90.4	NC	NC
M59	10.8	8	70.1	NC	NC
M33 (M5)	7.07	1	3.54	NC	NC
M17 (M4)	7.04	0.5	1.76	NC	NC
Total radioactivity	369	2	41957	NR[a]	201

AUC_{∞} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{tlast} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; NC = not calculable; NR = not reportable; $t_{1/2}$ = apparent terminal elimination half life; t_{max} = time of the maximum observed concentration.
[a] AUC % extrapolated >30%.
[b] r^2-adjusted value <0.7.
Source: Table 9 of Study INS1007-103 CSR

14.2.6. Study INS1007-104

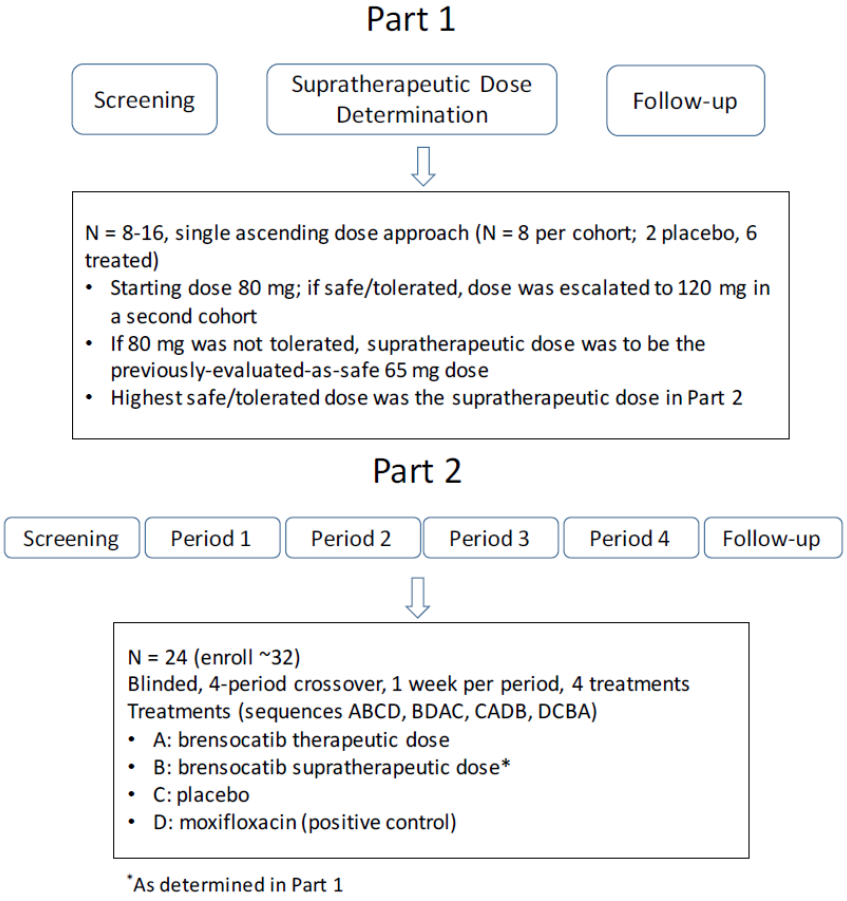
Title

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

Study Design

This was a 2-part, single-center, randomized, double-blind study in healthy male and female subjects to determine the supratherapeutic dose of brensocatib (Part 1) and to estimate the effects of single oral doses of brensocatib on the QT interval/QTc (Part 2). In Part 2, moxifloxacin was used as a positive control in a blinded manner. Part 2 was conducted after supratherapeutic dose determination in Part 1.

Figure 35. Study Design (Study INS1007-104)



Source: Figure 1 of Study INS1007-104 CSR

Study Formulation

Brensocatib 40-mg film-coated tablets (Batch CFNXV).

Sampling

- Parts 1 and 2: Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 168 (part 2) hours postdose

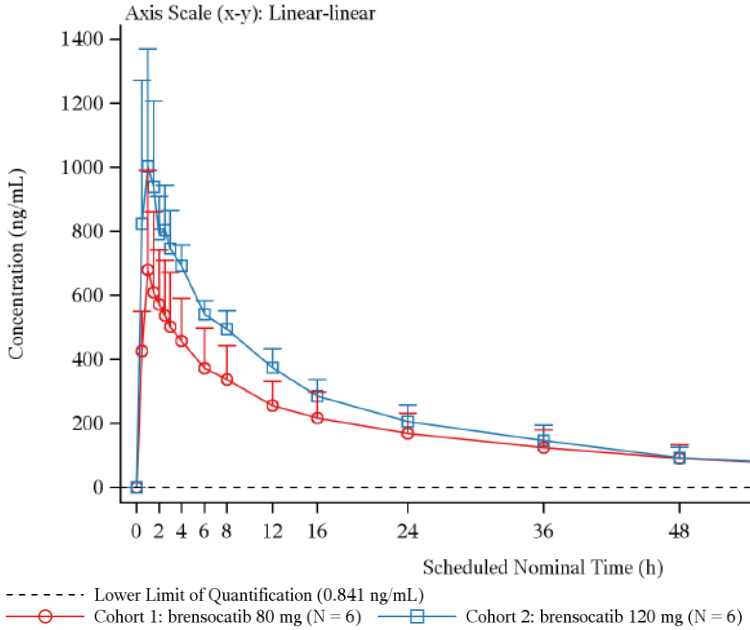
Results

The IRT-QT team has reviewed this study and concluded that brensocatib did not prolong the QT interval by Fridericia (QTcF) interval in this Thorough QT study. Refer to IND 133790 IRT-QT Study Review dated 02/21/2024 for details.

Part 1 PK Results

Following a single dose administration at doses of 80 mg and 120 mg brensocatib in healthy subjects, the median T_{max} is 1 hour and 1.28 hours, respectively, and the mean $T_{1/2}$ is 26.2 hours and 23.6 hours, respectively.

Figure 36. Arithmetic Mean (+SD) Concentration Profiles for Brensocatib in Plasma After Single Oral Administration of 80 and 120 mg Brensocatib



Source: Adapted from Figure 9 of Study INS1007-104 CSR

Table 76. Summary of Brensocatib Plasma PK Parameters After Single Oral Administration of 80 and 120 mg Brensocatib

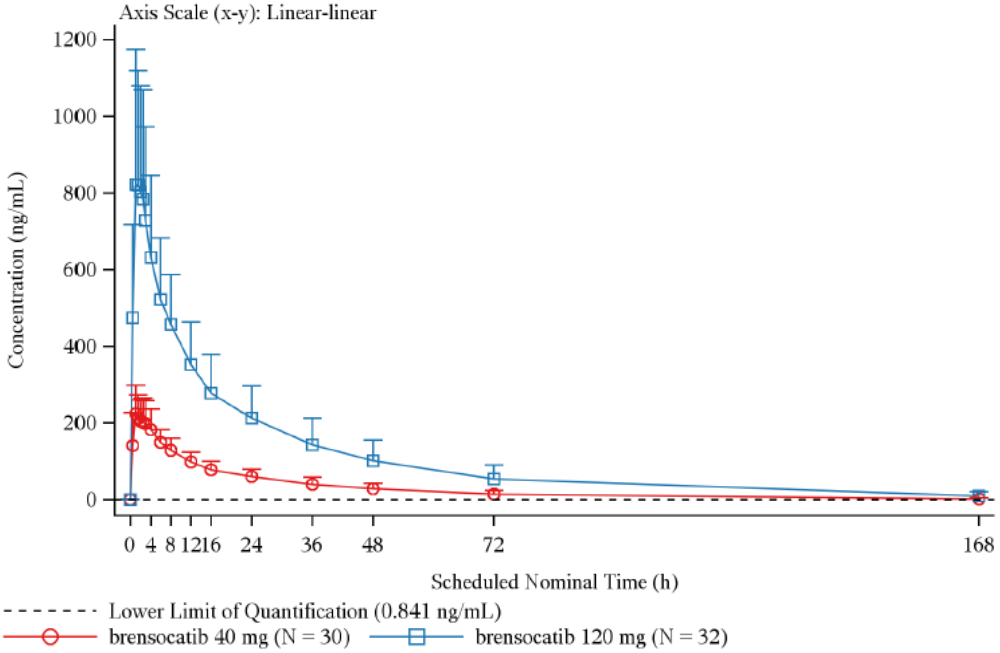
Parameter	Cohort 1: Brensocatib 80 mg (N = 6; n = 6)	Cohort 2: Brensocatib 120 mg (N = 6; n = 6)
AUC_{tlast} (h*ng/mL)	11900 (36.6)	15500 (15.9)
AUC_{0-72} (h*ng/mL)	11900 (36.6)	15500 (15.9)
AUC_{∞} (h*ng/mL)	14000 (39.8)	17500 (22.5)
C_{max} (ng/mL)	702 (41.3)	1130 (28.1)
T_{max} (h)	1.00 (1.00-2.53)	1.28 (0.500-3.00)
T_{last} (h)	72.0 (72.0-72.0)	72.0 (72.0-72.1)
$t_{1/2}$ (h)	26.2 (20.1)	23.6 (32.7)
CL/F (L/h)	7.02 (56.7)	7.15 (23.1)
V_z/F (L)	243 (35.6)	231 (14.4)
$DAUC_{tlast}$ (h*ng/mL/mg)	149 (36.6)	129 (15.9)
$DAUC_{0-72}$ (h*ng/mL/mg)	149 (36.6)	129 (15.9)
$DAUC_{\infty}$ (h*ng/mL/mg)	175 (39.8)	146 (22.5)
DC_{max} (ng/mL/mg)	8.78 (41.3)	9.38 (28.1)

AUC_{∞} = area under the concentration-time curve from time zero extrapolated to infinity; AUC_{0-72} = area under the concentration-time curve from time zero to 72 hours postdose; AUC_{tlast} = area under the concentration-time curve from time zero to time of last quantifiable concentration; CL/F = total clearance following extravascular administration; C_{max} = maximum observed plasma concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; $t_{1/2}$ = elimination half-life; T_{last} = time of the last quantifiable concentration; T_{max} = time of maximum observed plasma concentration; V_z/F = volume of distribution at terminal phase following extravascular administration.
Parameter starting with letter 'D' signifies the corresponding parameter was normalized by dose administered.
Arithmetic mean (CV) statistics are presented; for T_{max} and T_{last} median (minimum-maximum) statistics are presented.
Note: Because T_{last} is approximately 72 hours, AUC_{0-72} and AUC_{tlast} are identical.
Source: Table 16 of Study INS1007-104 CSR

Part 2 PK Results

Following a single dose administration at doses of 40 mg and 120 mg brensocatib in healthy subjects, the median T_{max} is 1.25 hours and 1.28 hours, respectively, and the mean $T_{1/2}$ is 24.3 hours and 25.2 hours, respectively.

Figure 37. Arithmetic Mean (+SD) Concentration Profiles for Brensocatib in Plasma After Single Oral Administration of 40 and 120 mg Brensocatib



Source: Adapted from Figure 10 of Study INS1007-104 CSR

Table 77. Summary of Brensocatib Plasma PK Parameters After Single Oral Administration of 40 and 120 mg Brensocatib

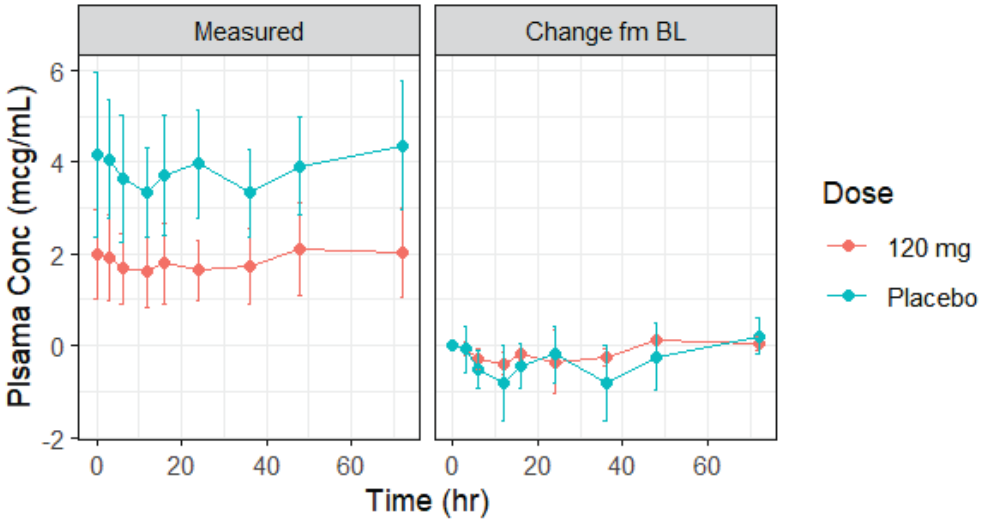
Parameter	Brensocatib 40 mg (N = 30; n = 26)	Brensocatib 120 mg (N = 32; n = 32)
AUC_{tlast} (h*ng/mL)	4440 (32.9)	15600 (38.1)
AUC_{0-72} (h*ng/mL)	4220 (30.1)	15000 (34.6)
AUC_{∞} (h*ng/mL)	4840 (34.9)	17400 (40.0)
C_{max} (ng/mL)	238 (31.3)	887 (36.0)
T_{max} (h)	1.25 (0.500-4.00)	1.28 (0.500-3.00)
T_{last} (h)	72.0 (72.0-168)	72.0 (72.0-168)
$t_{1/2}$ (h)	24.3 (31.8)	25.2 (34.4)
CL/F (L/h)	9.31 (35.5)	8.11 (41.2)
V_z/F (L)	301 (23.8)	267 (28.8)
$DAUC_{tlast}$ (h*ng/mL/mg)	111 (32.9)	130 (38.1)
$DAUC_{0-72}$ (h*ng/mL/mg)	105 (30.1)	125 (34.6)
$DAUC_{\infty}$ (h*ng/mL/mg)	121 (34.9)	145 (40.0)
DC_{max} (ng/mL/mg)	5.95 (31.3)	7.39 (36.0)

AUC_{∞} = area under the concentration-time curve from time zero extrapolated to infinity; AUC_{0-72} = area under the concentration-time curve from time zero to 72 hours postdose; AUC_{tlast} = area under the concentration-time curve from time zero to time of last quantifiable concentration; CL/F = total clearance following extravascular administration; C_{max} = maximum observed plasma concentration; CV = coefficient of variation (%); n = number of subjects with valid observations; N = number of subjects; $t_{1/2}$ = elimination half-life; T_{last} = time of the last quantifiable concentration; T_{max} = time of maximum observed plasma concentration; V_z/F = volume of distribution at terminal phase following extravascular administration.
Parameter starting with letter 'D' signifies the corresponding parameter was normalized by dose administered.
Arithmetic mean (CV) statistics are presented; for T_{max} and T_{last} median (minimum-maximum) statistics are presented.
Note: Because AUC_{tlast} included 168 hours postdose in some profiles, AUC_{0-72} and AUC_{tlast} are not identical in this analysis.
Source: Table 17 of Study INS1007-104 CSR

Metabolite Thiocyanate (M8) PK Results (Report VV-NC-000803)

A total of 72 plasma samples collected from the 120-mg dose group in Part 1 were analyzed to assess thiocyanate exposure, where 18 samples were from the placebo group (n = 2) and 54 samples were from the 120-mg dose group (n = 6). Thiocyanate plasma concentrations were 0.72 to 3.43µg/mL in the brensocatib group and 2.65 to 5.42µg/mL in the placebo group. Baseline-corrected concentrations were −1.75 to 0.238µg/mL in the brensocatib group versus −1.41 to 0.487µg/mL in the placebo group. The data indicate little change in thiocyanate concentrations following administration of a single dose of 120 mg (4.8 times the highest recommended dose of 25 mg).

Figure 38. Mean (± SD) Plasma Concentration Profiles of Thiocyanate in Healthy Subjects Following a Single Oral Administration of Brensocatib 120 mg or Placebo (Study INS1007-104)



Source: Figure 1 of Report VV-NC-000803

Table 78. Measured and Baseline-Corrected Thiocyanate Plasma Concentrations by Treatment in Healthy Subjects, Study INS1007-104

	Measured Concentration (µg/mL)		Baseline-corrected Concentration (µg/mL)	
	120 mg	Placebo	120 mg	Placebo
N of Subjects	54	18	54	18
N of Samples	6	2	6	2
mean	1.83	3.83	-0.157	-0.320
SD	0.82	1.00	0.312	0.546
median	1.51	3.69	-0.076	-0.224
Range	0.72-3.43	2.65-5.42	-1.75 -0.238	-1.41-0.487

Source: Table 1 of Report VV-NC-000803

14.2.7. Study INS1007-105

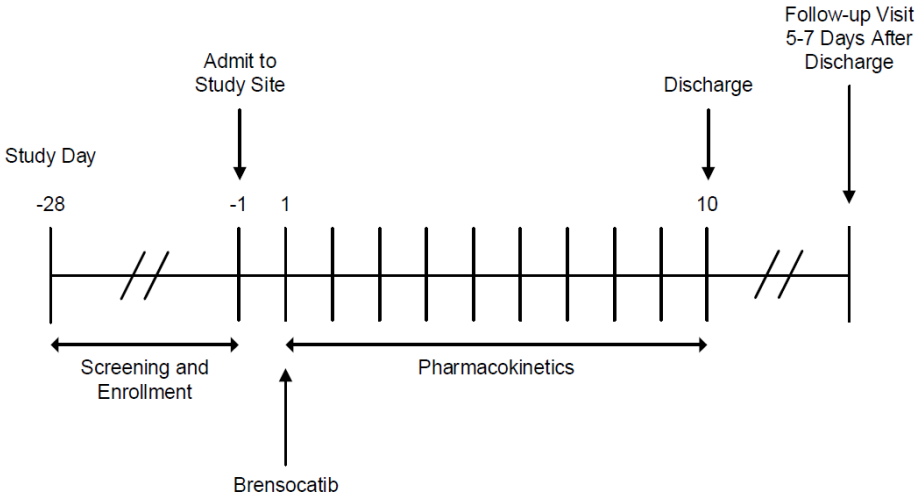
Title

An Open-label, Phase 1 Study to Evaluate the Pharmacokinetics and Safety of a Single Dose of Brensocatib in Subjects with Normal Hepatic Function and Subjects with Hepatic Impairment

Study Design

This was an open-label, multi-site, single-dose, parallel-group study to determine the PK, safety, and tolerability of brensocatib administered at 25 mg to fasted (at least 8 hours) male and female subjects with varying degrees of hepatic function compared to matched subjects with normal hepatic function. Hepatic impairment was classified by the numerical Child-Pugh score of hepatic impairment and grouped into mild (Child-Pugh score of 5 to 6), moderate (Child-Pugh score of 7 to 9), or severe (Child-Pugh score of 10 to 15) based on the Child-Pugh classification.

Figure 39. Study Design (INS1007-105)



Source: Figure 1 of Study INS1007-105 CSR

Study Formulation

Brensocatib film-coated tablets containing 25 mg brensocatib (batch number CMCYG).

Sampling

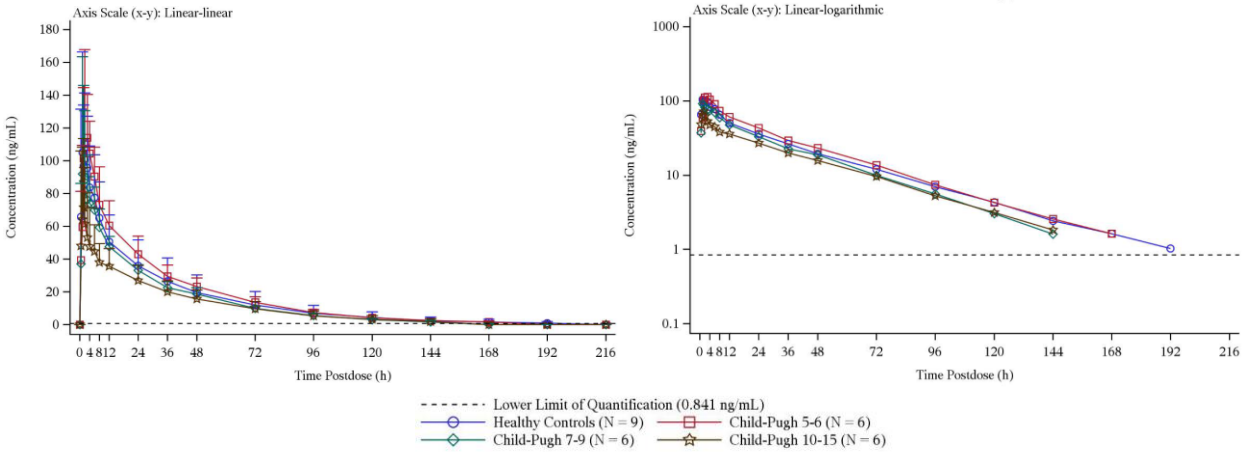
- Blood samples were collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours postdose
- Samples for plasma protein binding assessment were collected predose and 4 and 24 hours postdose
- Urine samples were collected predose (spot collection) and 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, and 192 to 216 hours postdose

Results

Six subjects in each hepatic impairment group completed the study. The median (min, max) Child-Pugh score was 5.5 (5.0, 6.0) for subjects with mild hepatic impairment (Child-Pugh 5-6), 7.5 (7.0, 9.0) for subjects with moderate hepatic impairment (Child-Pugh 7-9), and 10.5 (10.0, 12.0) for subjects with severe hepatic impairment (Child-Pugh 10-15).

Following single dose administration of 25 mg brensocatib, compared with subjects with normal hepatic function, C_{max} and AUC of total brensocatib increased by 12% and 20%, respectively, in subjects with mild hepatic impairment (Child-Pugh 5-6), remained comparable in subjects with moderate hepatic impairment (Child Pugh 7-9), and decreased by 26% and 20%, respectively, in subjects with severe hepatic impairment (Child-Pugh 10-15). No clinically relevant change in unbound exposure was observed between subjects with normal hepatic function and hepatic impairment (geometric mean ratio PK parameters ≤1.18). The mean fraction unbound in subjects with severe hepatic impairment appears greater than that in subjects with normal hepatic function (about 27% versus 18%). However, it is unclear whether this is a true difference given the small sample size and variability in the measurements.

Figure 40. Arithmetic Mean Concentration-Time Profiles of Total Brensocatib in Subjects With Hepatic Impairment or Normal Hepatic Function (Linear [+SD] and Semi-Logarithmic Scale)



Source: Figure 2 of Study INS1007-105 CSR

Table 79. Summary of Brensocatib (Total and Unbound) PK Parameters (Plasma and Urine) in Subjects With Hepatic Impairment or Normal Hepatic Function

Parameter	Healthy Controls (N = 9)	Child-Pugh 5-6 (N = 6)	Child-Pugh 7-9 (N = 6)	Child-Pugh 10-15 (N = 6)
AUC_{tlast} (h*ng/mL)	2930 (48.1)	3210 (12.4)	2510 (10.9)	2050 (38.3)
AUC_{∞} (h*ng/mL)	2980 (47.7)	3370 (16.2)	2570 (10.4)	2120 (38.2)
C_{max} (ng/mL)	122 (40.7)	133 (21.6)	113 (37.0)	90.7 (51.5)
t_{max} (h)	1.00 (1.00-3.00)	2.00 (1.50-3.00)	1.25 (1.00-6.00)	1.25 (0.500-24.0)
$t_{1/2}$ (h)	30.3 (26.6)	31.4 (24.5)	27.9 (14.5)	28.5 (24.3)
CL/F (L/h)	10.7 (58.5)	7.58 (16.5)	9.83 (10.2)	13.3 (37.7)
V_z/F (L)	413 (30.6)	353 (40.3)	396 (18.3)	515 (25.1)
f_{unb} (%)	17.8 (17.2)	16.9 (5.7)	19.7 (12.6)	26.9 (35.2)
$A_{e0-216h}$ [Total] (mg)	4.10 (36.6)	4.51 (37.1)[b]	4.77 (45.8)[a]	3.14 (7.7)[b]
$f_{e0-216h}$ [Total] (%)	16.4 (36.6)	18.0 (37.1)[b]	19.1 (45.8)[a]	12.5 (7.7)[b]
CL_R (L/h)	1.66 (48.0)	1.34 (39.4)	1.84 (41.3)[a]	1.72 (27.2)
$AUC_{tlast,unb}$ (h*ng/mL)	490 (36.2)	542 (11.1)	493 (12.7)	554 (49.0)
$AUC_{\infty,unb}$ (h*ng/mL)	500 (35.9)	569 (14.1)	503 (12.5)	572 (49.2)
$C_{max,unb}$ (ng/mL)	21.0 (31.4)	22.5 (21.2)	21.9 (31.9)	22.5 (56.1)
CL/F_{unb} (L/h)	57.6 (43.9)	44.7 (15.3)	50.4 (13.2)	55.3 (56.5)
V_z/F_{unb} (L)	2310 (25.2)	2080 (39.9)	2010 (11.5)	2070 (36.0)

Arithmetic Mean (arithmetic CV) statistics presented; for t_{max} median (min-max) statistics presented
$A_{e0-216h}$ [Total] and $f_{e0-216h}$ [Total] are urinary PK parameters, all others are plasma PK parameters.
[a] One subject's urine sample weight was missing between 0h and 6h, Ae not calculated and PK parameter underestimated; excluded from summary statistics.
[b] One subject in the Child-Pugh 5-6 group and 1 subject in the Child-Pugh 10-15 group did not complete the study and did not have all urine samples up to 216 hours collected.
Source: Table 9 of Study INS1007-105 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; SAD, single ascending dose; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 80. Statistical Analysis of the Total and Unbound PK Parameters in Subjects With Hepatic Impairment or Normal Hepatic Function

Parameter	Hepatic Impairment/ Child-Pugh score	n	GLSM	Test Versus Reference Ratio of GLSMs (90% CI)
AUC_{tlast} (ng*h/mL)	Healthy Controls (Reference)	6	2730	
	Child-Pugh 5-6 (Test)	6	3190	1.17 (0.715, 1.90)
	Healthy Controls (Reference)	6	2430	
	Child-Pugh 7-9 (Test)	6	2500	1.03 (0.690, 1.54)
	Healthy Controls (Reference)	6	2410	
	Child-Pugh 10-15 (Test)	6	1930	0.802 (0.495, 1.30)
AUC_{∞} (ng*h/mL)	Healthy Controls (Reference)	6	2780	
	Child-Pugh 5-6 (Test)	6	3330	1.20 (0.732, 1.96)
	Healthy Controls (Reference)	6	2480	
	Child-Pugh 7-9 (Test)	6	2560	1.03 (0.692, 1.54)
	Healthy Controls (Reference)	6	2460	
	Child-Pugh 10-15 (Test)	6	1990	0.810 (0.500, 1.31)
C_{max} (ng/mL)	Healthy Controls (Reference)	6	117	
	Child-Pugh 5-6 (Test)	6	131	1.12 (0.771, 1.63)
	Healthy Controls (Reference)	6	111	
	Child-Pugh 7-9 (Test)	6	106	0.960 (0.670, 1.38)
	Healthy Controls (Reference)	6	105	
	Child-Pugh 10-15 (Test)	6	77.8	0.741 (0.437, 1.26)
$AUC_{tlast,unb}$ (ng*h/mL)	Healthy Controls (Reference)	6	479	
	Child-Pugh 5-6 (Test)	6	539	1.13 (0.774, 1.64)
	Healthy Controls (Reference)	6	428	
	Child-Pugh 7-9 (Test)	6	489	1.14 (0.845, 1.55)
	Healthy Controls (Reference)	6	425	
	Child-Pugh 10-15 (Test)	6	496	1.17 (0.717, 1.90)
$AUC_{\infty,unb}$ (ng*h/mL)	Healthy Controls (Reference)	6	487	
	Child-Pugh 5-6 (Test)	6	564	1.16 (0.793, 1.69)
	Healthy Controls (Reference)	6	437	
	Child-Pugh 7-9 (Test)	6	500	1.14 (0.847, 1.55)
	Healthy Controls (Reference)	6	435	
	Child-Pugh 10-15 (Test)	6	511	1.18 (0.723, 1.91)
$C_{max,unb}$ (ng/mL)	Healthy Controls (Reference)	6	20.4	
	Child-Pugh 5-6 (Test)	6	22.1	1.08 (0.803, 1.46)
	Healthy Controls (Reference)	6	19.5	
	Child-Pugh 7-9 (Test)	6	20.8	1.07 (0.767, 1.48)
	Healthy Controls (Reference)	6	18.6	
	Child-Pugh 10-15 (Test)	6	20.0	1.08 (0.710, 1.63)

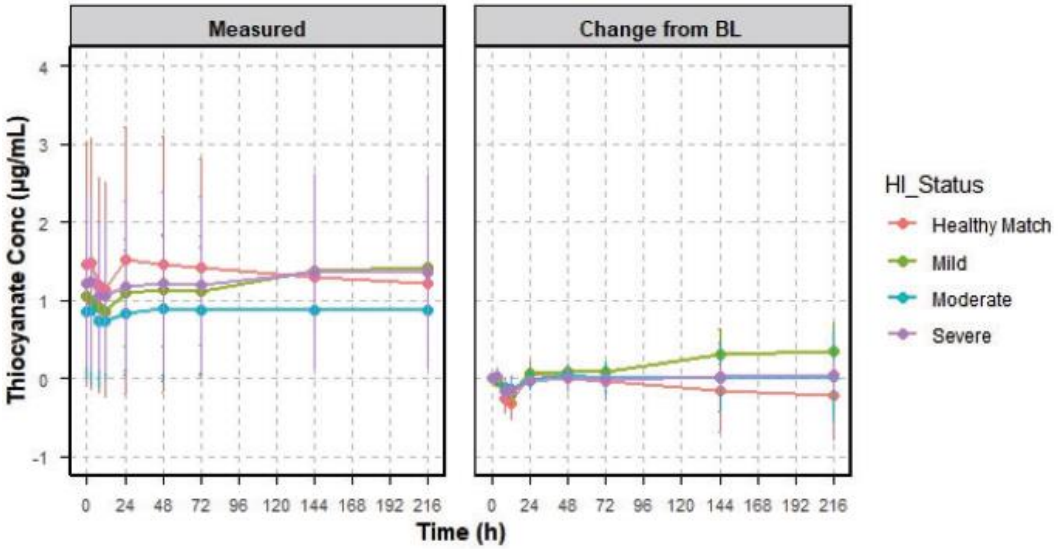
Source: Table 10 of Study INS1007-105 CSR
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least squares means; n, number of subjects; PK, pharmacokinetic

Metabolite Thiocyanate (M8) PK Results (Report VV-NC-000892)

A total of 239 plasma samples were analyzed, including 81 samples from the normal-matched group (n=9 subjects) and 158 samples from the hepatic impairment groups (n=18 subjects). The thiocyanate plasma concentrations in all groups were below the Applicant-defined upper limit of

the normal range (i.e., 15µg/mL), with the highest observed value being 5.83µg/mL (observed in a subject with normal hepatic function). Baseline-corrected concentrations for all groups fluctuated around zero (−0.102 to 0.0429µg/mL) over time, indicating little change in thiocyanate concentrations following a single dose of 25 mg brensocatib. There was no apparent trend for change in thiocyanate concentration with increasing severity of hepatic impairment.

Figure 41. Mean (± SD) Plasma Concentration Profiles of Thiocyanate Over Time in Subjects With Hepatic Impairment and Healthy Subjects Following a Single Oral Administration of Brensocatib at 25 mg (Study INS1007-105)



Source: Figure 1 of Report VV-NC-000892

Table 81. Thiocyanate Plasma Concentrations in Hepatically Impaired Subjects and Normal Subjects, Study INS1007-105

	Mild	Moderate	Severe	NM
N of Sample	52	54	52	81
N of Subject	6	6	6	9
Measured Thiocyanate Concentrations (µg/mL)				
Mean (SD)	1.09 (0.692)	0.836 (0.772)	1.20 (1.02)	1.35 (1.38)
median	0.800	0.427	0.950	0.822
Range	0.356 – 2.72	0.0756* – 2.69	BLQ – 2.81	0.241 – 5.83
Baseline-corrected *Thiocyanate Concentrations (µg/mL)*				
Mean (SD)	0.0429 (0.229)	-0.0215 (0.260)	-0.0364 (0.134)	-0.102 (0.320)
median	0.00	-0.0560	-0.0200	-0.0240
Range	-0.520 – 0.760	-0.590 – 1.16	-0.400 – 0.340	-1.48 – 0.450

BLQ = below limit of quantification (<0.200 µg/mL)
* Extrapolated value below the limit of quantification
Source: Table 1 of Report VV-NC-000892
Abbreviation: NM, normal matched

14.2.8. Study INS1007-106

Title

A Phase 1, Open label, Fixed Sequence Study to Assess the Pharmacokinetics of Brensocatib when Administered Alone and With Multiple Doses of Rifampin (CYP3A Inducer) or Esomeprazole (Proton Pump Inhibitor) in Healthy Subjects

Study Design

This study was an open label, fixed sequence, 2-part, 2-period study to determine the PK, safety, and tolerability of brensocatib when administered alone and in combination with multiple doses of rifampin (Part 1) or esomeprazole (Part 2) in healthy subjects (n=32, 16/part).

Part 1: Subjects in Part 1 received the following treatments after an overnight fast (at least 8 hours):

- Period 1 (Treatment A)
  - Day 1: single oral dose of 25 mg brensocatib
- Period 2 (Treatment B)
  - Days 8 to 16: oral doses of 600 mg rifampin QD
  - Day 17: a single oral dose of 25 mg brensocatib and an oral dose of 600 mg rifampin administered approximately 4 hours after the brensocatib dose
  - Days 18 to 23: rifampin 600 mg alone QD

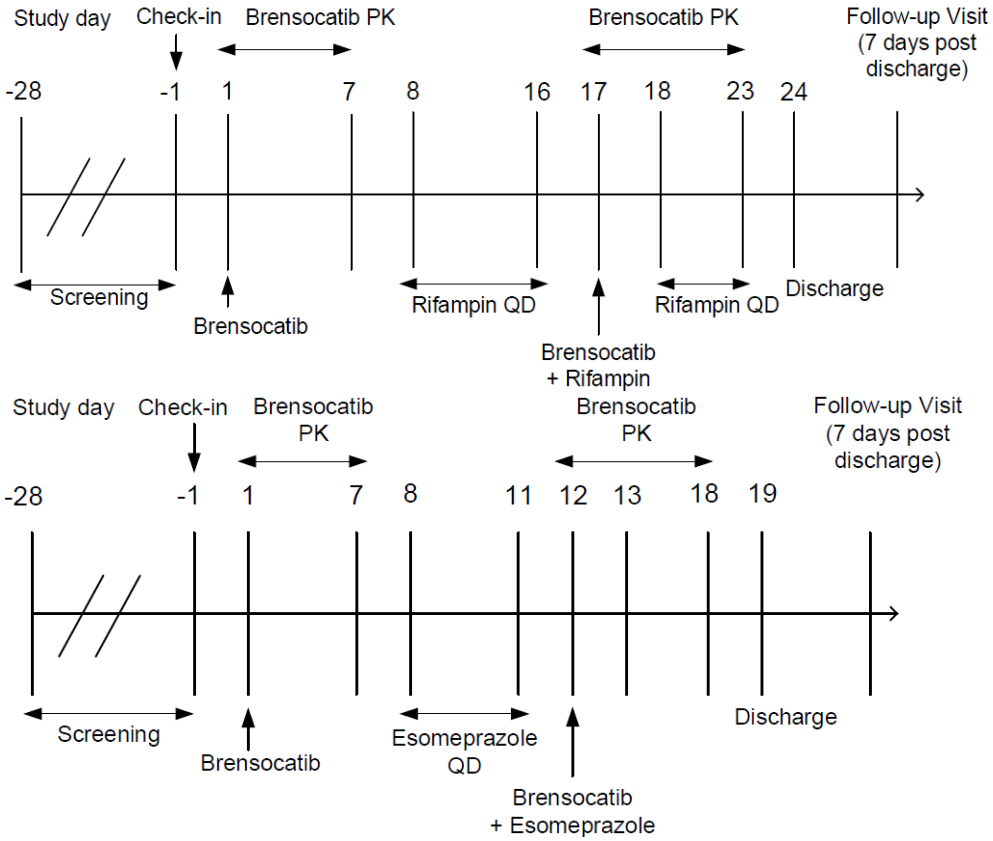
There was a washout period of at least 16 days between brensocatib dosing in Periods 1 and 2.

Part 2: Subjects in Part 2 received the following treatments after an overnight fast (at least 8 hours):

- Period 1 (Treatment C)
  - Day 1: single oral dose of 25 mg brensocatib
- Period 2 (Treatment D)
  - Days 8 to 11: oral doses of 40 mg esomeprazole QD
  - Day 12: a single oral dose of 25 mg brensocatib co-administered with an oral dose of 40 mg esomeprazole

There was a washout period of at least 11 days between brensocatib dosing in Periods 1 and 2.

Figure 42. Study Design of Part 1 (Upper Panel) and Part 2 (Lower Panel) (Study INS1007-106)



Source: adapted from Figures 1 and 2 of Study INS1007-106 CSR
Abbreviations: PK, pharmacokinetic; QD, once daily

Study Formulation

Brensocatib film-coated tablets containing 25 mg brensocatib (batch number CMPKH)

Sampling

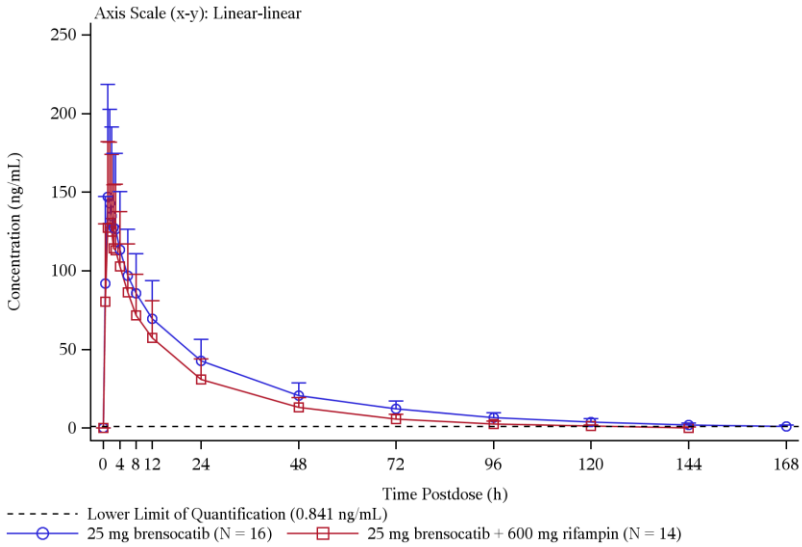
Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after brensocatib dosing

Results

When co-administered with rifampin (a CYP3A inducer), brensocatib C_{max} and AUC decreased by 15% and 33%, respectively, compared to when brensocatib was administrated alone. When co-administered with rifampin, the brensocatib half-life was reduced to about 21 hours compared to 27 hours when brensocatib was administered alone. The data indicate that there is a mild effect of CYP3A induction on brensocatib exposure.

When co-administered with esomeprazole (a proton pump inhibitor), brensocatib C_{max} and AUC was comparable to brensocatib administrated alone.

Figure 43. Arithmetic Mean (+SD) Plasma Concentration vs. Time Profiles of Brensocatib Following a Single Dose of Brensocatib Alone or in the Presence Rifampin



Source: adapted from Figure 3 of Study INS1007-106 CSR

Table 82. Summary of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Rifampin

Parameter	25 mg brensocatib (N = 16)	25 mg brensocatib + 600 mg rifampin (N = 14)
AUC_{tlast} (h*ng/mL)	3350 (35.0)	2390 (39.6)
AUC_{inf} (h*ng/mL)	3430 (34.0)	2430 (39.0)
C_{max} (ng/mL)	164 (39.2)	141 (36.9)
t_{max} (h)	1.50 (0.583-6.00)	1.50 (0.617-3.92)
t_{last} (h)	168 (72.0-168)	120 (47.9-168)
$t_{1/2}$ (h)	27.2 (13.0)	20.5 (23.2)
CL/F (L/h)	8.24 (39.0)	13.3 (67.2)
V_z/F (L)	314 (30.5)	343 (33.6)
Ratio_AUC_{inf}	---	0.683 (19.4)
Ratio_AUC_{tlast}	---	0.683 (19.7)
Ratio_C_{max}	---	0.861 (21.5)

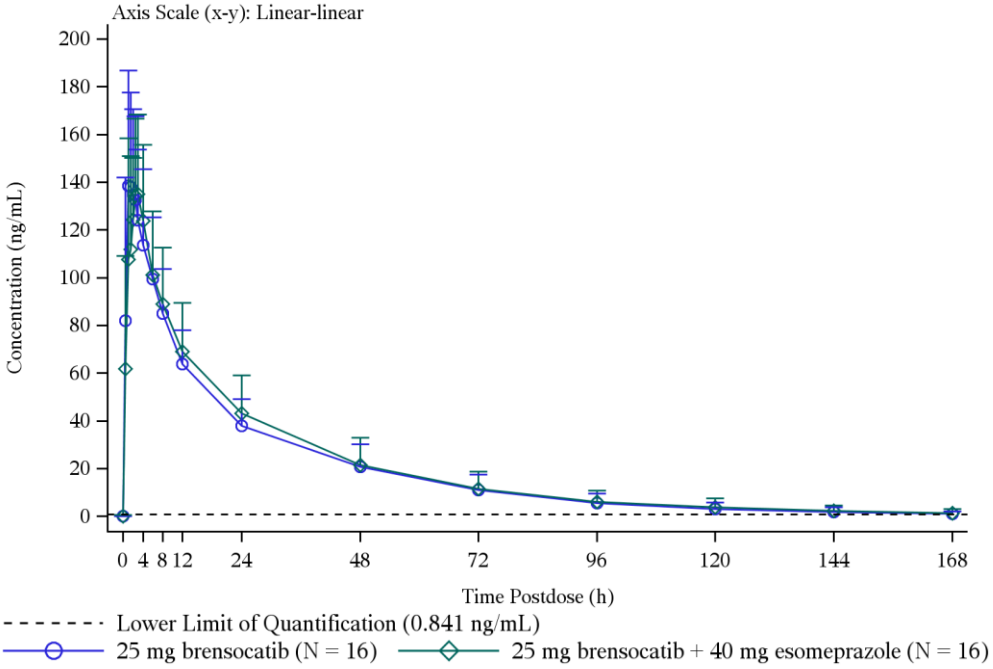
Source: Table 8 of Study INS1007-106 CSR
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 83. Statistical Analysis of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Rifampin

				Test versus Reference	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV%
AUC_{tlast} (h*ng/mL)	25 mg brensocatib (Reference)	16	3150	---	---
	25 mg brensocatib + 600 mg rifampin (Test)	14	2110	0.671 (0.606, 0.743)	15.4
AUC_{inf} (h*ng/mL)	25 mg brensocatib (Reference)	16	3240	---	---
	25 mg brensocatib + 600 mg rifampin (Test)	14	2170	0.670 (0.606, 0.741)	15.1
C_{max} (ng/mL)	25 mg brensocatib (Reference)	16	154	---	---
	25 mg brensocatib + 600 mg rifampin (Test)	14	130	0.846 (0.763, 0.938)	15.5
$t_{1/2}$ (h)	25 mg brensocatib (Reference)	16	27.0	---	---
	25 mg brensocatib + 600 mg rifampin (Test)	14	19.9	0.738 (0.675, 0.806)	13.4
$t_{1/2}$ (h)#	25 mg brensocatib (Reference)	14	27.2	---	---
	25 mg brensocatib + 600 mg rifampin (Test)	14	22.1	-6.38 (-7.85, -5.13)	---

The n, median, and Hodges-Lehmann estimate of median difference (90% CI).
Model: ln(parameter) = treatment + random error, with subject fitted as a random effect
The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the LSMs, differences in LSMs, and corresponding CIs on the ln scale.
Source: Table 9 of Study INS1007-106 CSR
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; CV%, coefficient of variation; GLSM, geometric least squares means; n, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life

Figure 44. Arithmetic Mean (+SD) Plasma Concentration vs. Time Profiles of Brensocatib Following a Single Dose of Brensocatib Alone or in the Presence of Esomeprazole



Source: Figure 4 of Study INS1007-106 CSR

Table 84. Summary of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Esomeprazole

Parameter	25 mg brensocatib (N = 16)	25 mg brensocatib + 40 mg esomeprazole (N = 16)
AUC_{tlast} (h*ng/mL)	3170 (32.4)	3360 (37.8)
AUC_{inf} (h*ng/mL)	3230 (32.6)	3450 (38.8)
C_{max} (ng/mL)	160 (26.6)	152 (22.2)
t_{max} (h)	1.25 (0.500-4.00)	2.50 (0.500-4.00)
t_{last} (h)	168 (95.7-168)	168 (95.8-168)
$t_{1/2}$ (h)	25.3 (28.3)	26.8 (31.8)
CL/F (L/h)	8.74 (39.7)	8.42 (41.8)
V_z/F (L)	296 (27.6)	297 (29.1)
Ratio_AUC_{inf}	---	1.05 (8.3)
Ratio_AUC_{tlast}	---	1.05 (8.1)
Ratio_C_{max}	---	0.982 (21.7)

Arithmetic mean (arithmetic CV) statistics presented; for t_{max} and t_{last} median (minimum-maximum) statistics presented.

Source: Table 10 of Study INS1007-106 CSR)
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life; Vz/F, apparent volume of distribution during terminal phase

Table 85. Statistical Analysis of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Esomeprazole

				Test versus Reference	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV%
AUC_{tlast} (h*ng/mL)	25 mg brensocatib (Reference)	16	2990	---	---
	25 mg brensocatib + 40 mg esomeprazole (Test)	16	3140	1.05 (1.01, 1.08)	5.51
AUC_{inf} (h*ng/mL)	25 mg brensocatib (Reference)	16	3050	---	---
	25 mg brensocatib + 40 mg esomeprazole (Test)	16	3210	1.05 (1.01, 1.09)	5.64
C_{max} (ng/mL)	25 mg brensocatib (Reference)	16	154	---	---
	25 mg brensocatib + 40 mg esomeprazole (Test)	16	148	0.959 (0.868, 1.06)	16.2

Model: ln(parameter) = treatment + random error, with subject fitted as a random effect
The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the LSMs, differences in LSMs, and corresponding CIs on the ln scale.
Source: Table 11 of Study INS1007-106 CSR
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least squares means; n, number of subjects; PK, pharmacokinetic

14.2.9. Study INS1007-109

Title

A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of Clarithromycin, a Strong CYP3A4 Inhibitor, on Brensocatib Pharmacokinetics in Healthy Subjects.

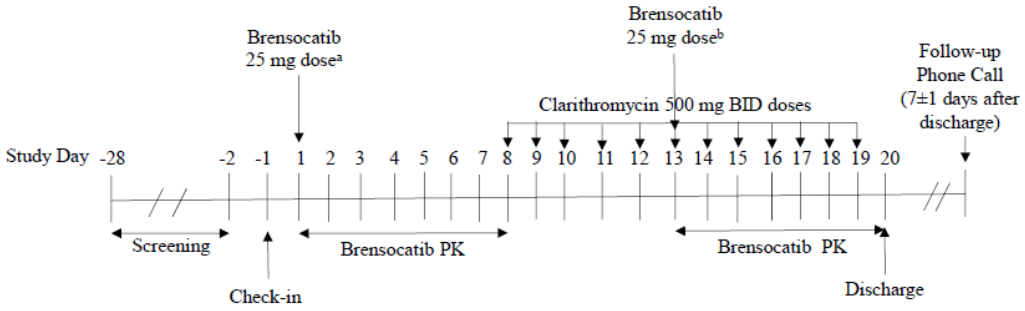
Study Design

This was a single-center, open-label, fixed-sequence study to investigate the effect of clarithromycin coadministration on the single-dose PK of brensocatib in healthy subjects (n=22). All subjects received each of the following treatments:

- Day 1: single dose of 25 mg brensocatib after an overnight fast of at least 8 hours
- Days 8 to 12: oral doses of 500 mg clarithromycin BID taken with food

- Day 13: single dose of 25 mg brensocatib co-administered with 500 mg clarithromycin in the morning after an overnight fast of at least 8 hours. A second 500 mg clarithromycin dose was administered 12 hours after the morning dose.
- Days 14 to 19: oral doses of 500 mg clarithromycin BID taken with food

Figure 45. Study Design (INS1007-109)



Abbreviations: BID = twice daily; PK = pharmacokinetic.
[a] Brensocatib dose was administered in the morning after an overnight fast of at least 8 hours.
[b] Brensocatib dose was coadministered with the morning clarithromycin dose after an overnight fast of at least 8 hours.

Source: Figure 1 of Study INS1007-109 CSR

Study Formulation

Brensocatib tablets 25 mg (lot number CMPKH)

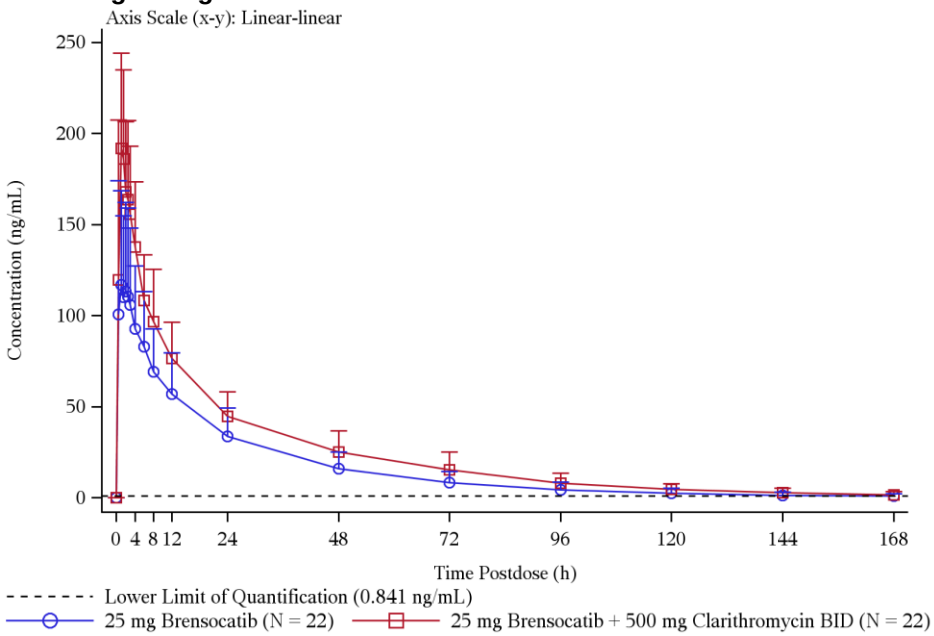
Sampling

Samples were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose on Day 1 and Day 13. On Day 8, the 168-hour PK samples should be obtained prior to the morning dose of clarithromycin.

Results

When co-administered with clarithromycin (a strong CYP3A4 inhibitor), brensocatib C_{max} and AUC increased by 68% and 56%, respectively, compared to when brensocatib was administrated alone.

Figure 46. Arithmetic Mean (+SD) Plasma Concentration vs. Time Profiles of Brensocatib Following a Single Dose of Brensocatib Alone or in the Presence of Clarithromycin



Source: adapted from Figure 2 of Study INS1007-109 CSR
Abbreviations: BID, twice daily; N, number of subjects; PK, pharmacokinetic

Table 86. Summary of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Clarithromycin

Parameter	25 mg Brensocatib (N = 22)	25 mg Brensocatib + 500 mg Clarithromycin BID (N = 22)
AUC_{tlast} (h*ng/mL)	2660 (48.0)	3920 (35.5)
AUC_{inf} (h*ng/mL)	2720 (48.5)	4010 (36.6)
C_{max} (ng/mL)	136 (44.6)	213 (23.9)
T_{max} (h)	1.52 (0.500-6.00)	1.00 (0.500-3.00)
T_{last} (h)	144 (72.0-168)	168 (119-168)
$t_{1/2}$ (h)	25.0 (29.1)	29.0 (17.6)
CL/F (L/h)	11.4 (47.4)	6.93 (31.3)
V_z/F (L)	370 (31.9)	280 (25.8)

Arithmetic Mean (arithmetic CV) statistics presented; for T_{max} and T_{last}, median (minimum-maximum) statistics presented.

Source: Table 6 of Study INS1007-109 CSR
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{last}, time of last measurable concentration; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase

Table 87. Statistical Analysis of Brensocatib PK Parameters Following a Single Dose of Brensocatib Alone or in the Presence of Clarithromycin

				Test versus Reference	
Parameter	Treatment	n	GLSM	Ratio of GLSMs (90% CI)	Within-subject CV
AUC_{tlast} (h*ng/mL)	25 mg Brensocatib (Reference)	22	2390	---	---
	25 mg Brensocatib + 500 mg Clarithromycin BID (Test)	22	3720	1.558 (1.456, 1.668)	13.1
AUC_{inf} (h*ng/mL)	25 mg Brensocatib (Reference)	22	2440	---	---
	25 mg Brensocatib + 500 mg Clarithromycin BID (Test)	22	3800	1.555 (1.455, 1.662)	12.9
C_{max} (ng/mL)	25 mg Brensocatib (Reference)	22	124	---	---
	25 mg Brensocatib + 500 mg Clarithromycin BID (Test)	22	207	1.675 (1.501, 1.870)	21.4
$t_{1/2}$ (h)#	25 mg Brensocatib (Reference)	22	24.8	---	---
	25 mg Brensocatib + 500 mg Clarithromycin BID (Test)	22	28.2	4.118 (2.486, 5.402)	---

The n, median, and Hodges-Lehmann estimate of median difference (90% CI) from the Wilcoxon signed-rank test presented.
Model: ln(parameter) = treatment + subject + random error, with subject fitted as a random effect
The GLSMs, ratios of GLSMs, and corresponding CIs were obtained by taking the exponential of the LSMs, differences in LSMs, and corresponding CIs on the ln scale.
Source: Table 7 of Study INS1007-109 CSR
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{last}, time of last measurable concentration; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase

14.2.10. Study 201

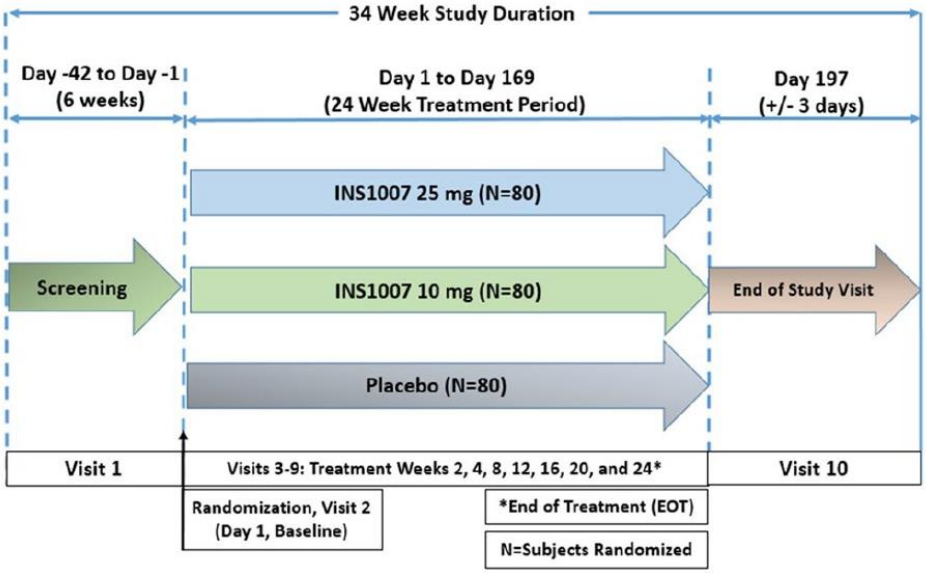
Title

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

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, global Phase 2 study in subjects with NCFB. It was planned that approximately 240 subjects would be randomized in a 1:1:1 ratio to 3 treatment arms (80/arm) to receive either 10 mg or 25 mg of INS1007 or placebo. The treatment period of the study was 24 weeks with a 4-week follow-up period. A PK substudy with intensive PK sampling was conducted at a select number of sites, with a maximum of 36 subjects.

Figure 47. Study Design, Study 201



Source: Figure 1 of Study INS1007-201 CSR
Abbreviations: EOT, end of treatment; N, number of subjects

Study Formulation

INS1007 film-coated tablet, 10 mg (L005917) and 25 mg (L005107, L009132)

Sampling

- PK Substudy: predose and 1, 2, 3, 4, 6, 8 hours postdose on Day 1 and Week 4. Predose at Weeks 2, 12, 24.
- Other Subjects: predose at Weeks 4, 12, 24

Results

INS1007 PK Results

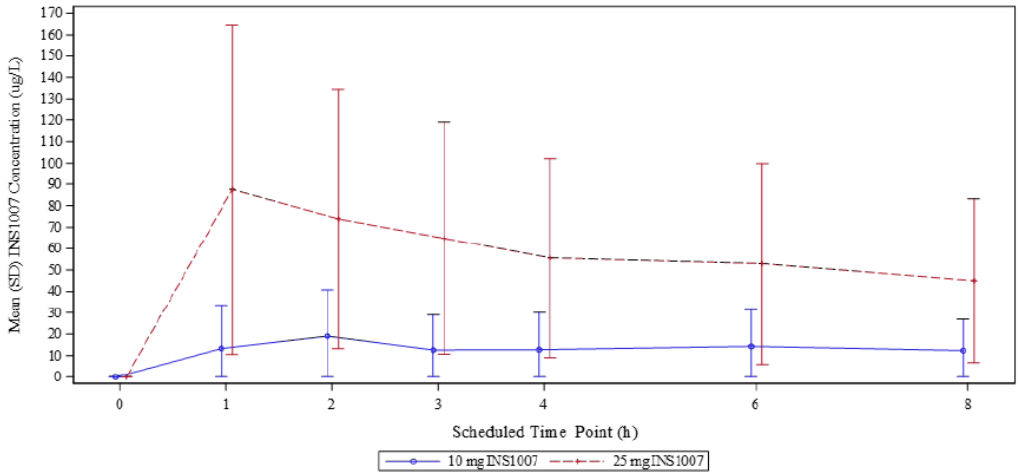
The PK data and PK profiles of INS1007 are shown as below. In general, the pharmacokinetics of brensocatib was comparable between healthy subjects and subjects with NCFB. Between doses of 10 mg and 25 mg, exposure increased in a roughly dose-proportional manner, with C_{max} values and trough concentrations increasing by about 2.3- to 2.9-fold for a 2.5-fold increase in dose.

Table 88. Summary of Mean Pre-Dose Plasma Concentrations for Intensely and Sparsely Sampled Subjects at Weeks 4, 12, and 24

	INS1007 10mg					INS1007 25 mg			
Sampling Sub-Population	**n**	**BLQ (n)**	**Mean (CV%) (ng/mL)**	**Range (ng/mL)**		**n**	**BLQ (n)**	**Mean (CV%) (ng/mL)**	**Range (ng/mL)**
Intense									
---Week 4	8	0	58.44 (38.6)	22.9-101		15	2	132.3 (78.0)	0.0-376
---Week 12	6	0	62.95 (52.5)	34.3-125		13	2	143.3 (71.4)	0.0-373
---Week 24	10	0	60.33 (62.0)	10.9-135		12	2	139.1 (85.2)	0.0-419
Sparse									
---Week 4	49	1	64.91 (43.0)	0.0-141		53	0	182.1 (52.2)	8.08-468
---Week 12	50	1	65.96 (49.1)	0.0-161		55	0	191.1 (45.7)	36.8-423
---Week 24	56	2	63.77 (64)	0.0-173		54	3	166.9 (62.9)	0.0-437

Source: Table 14.2.2.1
Notes: PK concentrations BLQ in pre-dose samples and in samples taken before the time of the first quantifiable value were set to zero; Post-dose BLQ values after the first quantifiable time point were set to zero.
BLQ = Below the Limit of Quantification (0.250 ug/L); CV = coefficient of variation; PK = pharmacokinetic(s)
Source: Table 26 of Study INS1007-201 CSR

Figure 48. Mean Plasma Concentration Profiles for INS1007 vs. Time by Dose on Day 1 (PK Substudy/Intense Sampling, Linear Scale)



Source: Figure 7 of Study INS1007-201 CSR
Abbreviations: h, hour; PK, pharmacokinetic

Table 89. Summary of INS1007 PK Parameters in PK Substudy

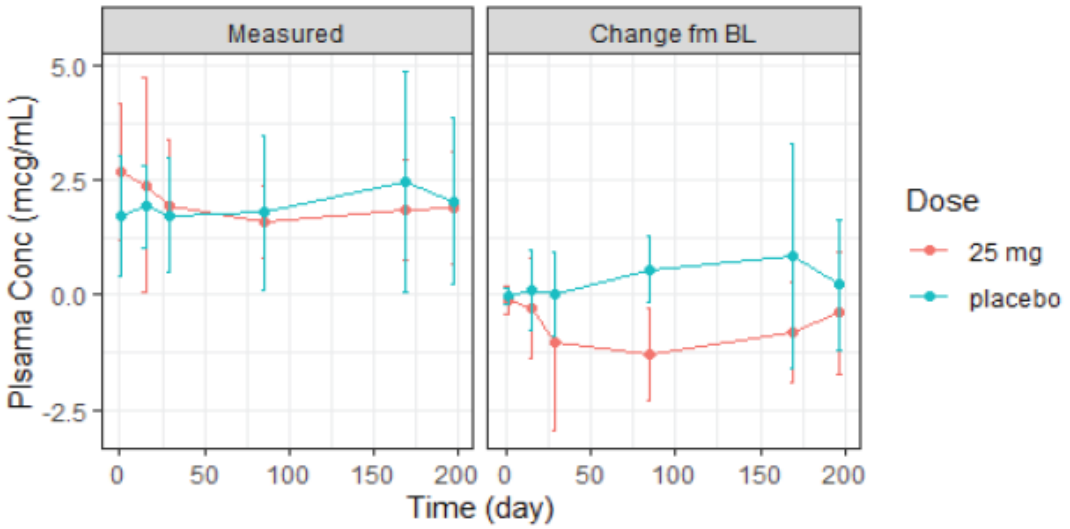
PK parameter	Summary Statistics	INS1007 10 mg (N=11)		INS1007 25 mg (N=16)	
		Day 1	Day 29	Day 1	Day 29
t_{max} (h)	n	8	8	12	12
	Median (min,max)	0.55 (0.0, 2.0)	2.9 (1.0, 8.0)	1.0 (0.0, 6.0)	1.1 (0.0, 4.0)
C_{max} (ng/mL)	n	8	8	12	12
	Mean (CV%)	21.23 (110.0)	80.11 (32.8)	96.58 (79.9)	218.9 (62.2)
RC_{max} (ng/mL)	n	--	4	--	8
	Mean (CV%)	--	2.198 (16.3)	--	1.980 (41.2)
C_{min} (ng/mL)	n	8	8	12	12
	Mean (CV%)	0.000 (-)	58.66 (38.8)	0.000 (-)	119.9 (75.1)
AUC_{0-8} (h*ng/mL)	n	8	7	11	11
	Mean (CV%)	114.4 (114.4)	529.9 (32.4)	428.7 (87.1)	1298 (62.5)
$RAUC_{0-8}$ (h*ng/mL)	n	--	3	--	7
	Mean (CV%)	--	2.742 (11.8)	--	2.525 (48.2)
AUC_{last} (h*ng/mL)	n	4	8	8	11
	Mean (CV%)	226.7 (30.3)	568.7 (34.5)	686.5 (27.4)	1513 (52.3)

Source: Table 27 of Study INS1007-201 CSR
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; R, Ratio Day 29:Day1; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration

INS1007 Metabolite Thiocyanate (M8) PK Results (Report VV-NC-000801)

A total of 215 plasma samples collected at up to Day 197 were analyzed, including 90 samples from the placebo group and 125 samples from the 25 mg brensocatib dose group. Thiocyanate concentrations were generally comparable between brensocatib 25-mg group (0.39 to 6.52µg/mL) and placebo group (0.19 to 7.90µg/mL). The mean change-from-baseline thiocyanate concentrations were generally low for both groups.

Figure 49. Mean (± SD) Plasma Concentration Profiles of Thiocyanate in Subjects With NCFB Following Once-Daily Administration of Brensocatib 25 mg or Placebo for 26 Weeks, Trial 201



Source: Figure 1 of Report No. VV-NC-000801
Abbreviations: BL, baseline; NCFB, non-cystic fibrosis bronchiectasis

Table 90. Summary of Measured and Baseline-Corrected Thiocyanate Plasma Concentrations by Treatment in NCFB Subjects, Trial 201

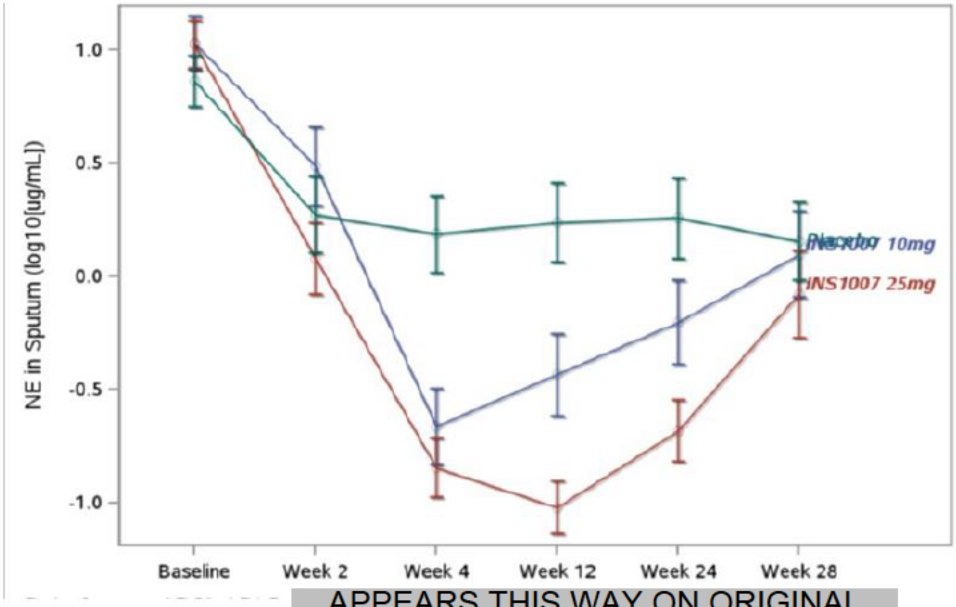
	Measured Concentration (µg/mL)		Baseline-corrected Concentration (µg/mL)	
	25 mg	Placebo	25 mg	Placebo
N of Sample	125	90	71	76
N of Subject	26	17	9	10
mean	2.00	1.89	-0.67	0.17
SD	1.37	1.53	1.40	1.07
median	1.64	1.42	-0.42	0.00
Range	0.39-6.52	0.19-7.90	-5.4 – 2.1	-1.9 – 5.3

Source: Figure 1 of Report No. VV-NC-000801
Abbreviation: NCFB, non-cystic fibrosis bronchiectasis

PD Results

The concentration of NE in sputum was a secondary efficacy endpoint for the study. In the PD population (n = 80 in 10-mg group, n = 89 in 25-mg group, n = 84 in placebo group), mean concentrations of NE in sputum appeared to decline in a dose-dependent manner in the two INS1007 treatment groups over the 24-week treatment period. After treatment cessation, NE sputum concentrations approached baseline ranges within 4 weeks. No INS1007 effect on blood NE concentrations was observed.

Figure 50. Mean Concentrations (Log 10) of NE in Sputum Over Time



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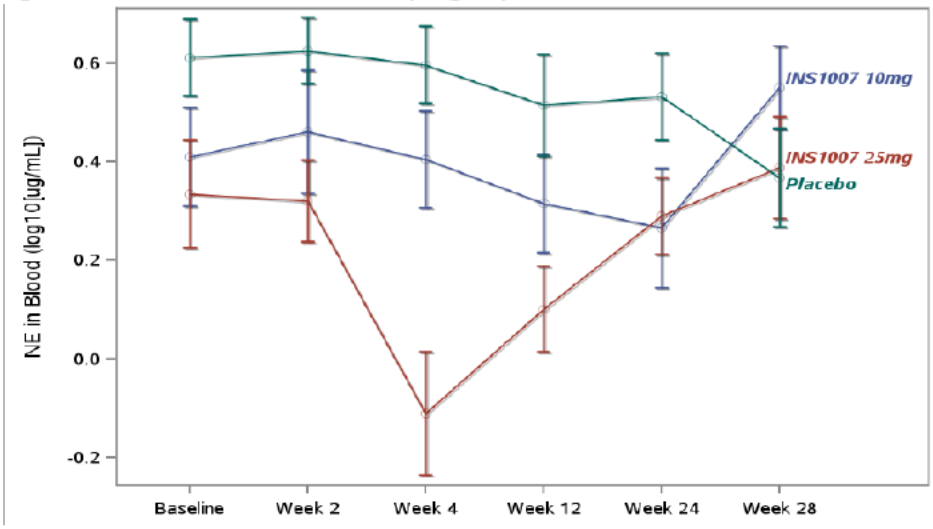
Source: Figure 14.2.3.3.1g
NE = neutrophil elastase; SE = standard error
Source: Figure 9 of Study INS1007-201 CSR

Figure 51. Mean Concentrations (Log 10) of NE in Blood Over Time



Source: Figure 14.2.3..3.3.1c
NE = neutrophil elastase; SE = standard error
Source: Figure 12 of Study INS1007-201 CSR

14.2.11. Trial 301

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis-The ASPEN Study.

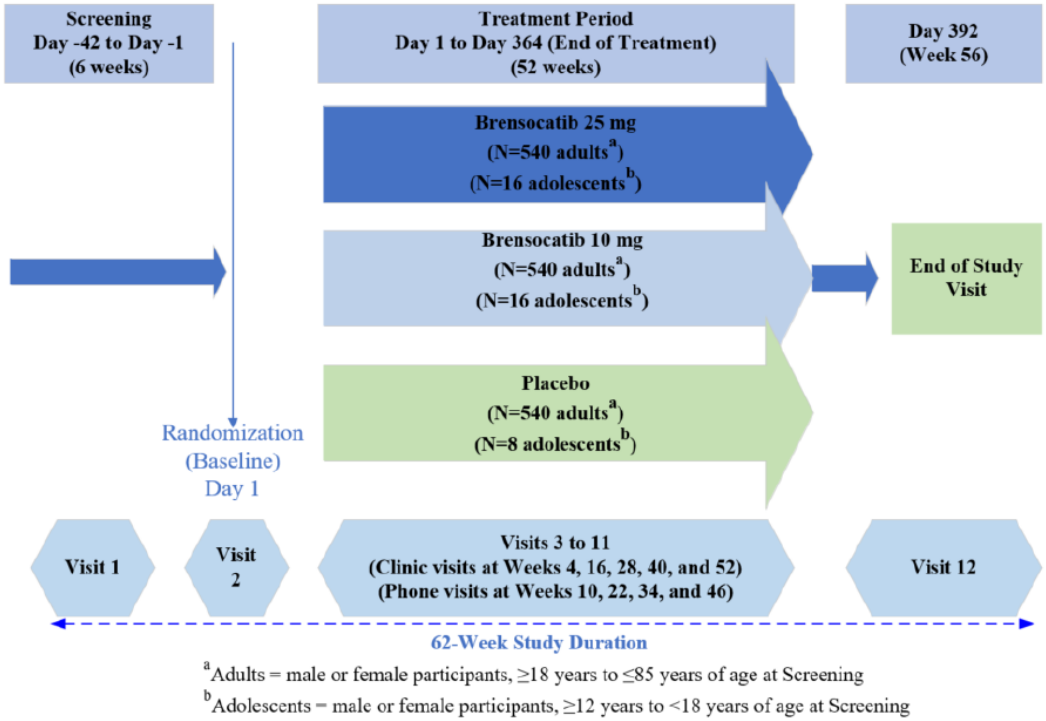
Study Design

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study in adult and adolescent subjects with NCFB. The study was designed to randomize approximately 1620 adults in a 1:1:1 ratio to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD for 52 weeks (540 subjects per arm). 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 QD, brensocatib 25 mg QD, or matching placebo QD for 52 weeks (16:16:8 participants per arm, respectively). There was no stratification for adolescents.

A PK/PD Substudy was designed to include approximately 300 adults not receiving cyclic antibiotics at baseline and from whom additional blood PK and sputum PD samples were collected.

For full study design details for Study 301, refer to Section 6.

Figure 52. Study Design, Trial 301



Source: Figure 1 of Study INS1007-301 CSR

Study Formulation

Brensocatib film-coated tablets, 10 mg and 25 mg

Sampling

- PK/PD Substudy: PK samples were collected from 126 adults who received brensocatib (62 in the 10-mg group, 64 in the 25-mg group) on Day 1 and Week 28 (predose, 0.5, 2, and 4 to

8 hours postdose), at Week 4 and Week 40 (predose and 2 hours postdose), and at Week 16 and Week 52 visits (predose only).

- Main Study: Following Global Amendment 3, collection of PK samples was expanded to all enrolled and newly enrolled adults in the "main study" regardless of cyclic antibiotic use at baseline. PK samples were collected from 402 adults (194 in the 10-mg group, 208 in the 25-mg group) at predose and 2 to 4 hours postdose on Day 1, Week 16, Week 28, and Week 40. Predose samples will also be collected at Week 4 and Week 52.
- Blood PD samples were collected from approximately 40 adult participants in the PK/PD substudy. Blood PK and sputum PD samples were collected from all adolescents not receiving cyclic antibiotics at baseline (blood PD samples were not collected from adolescents).

Results

PK Results

The mean brensocatib plasma concentrations over time in adults and adolescents with brensocatib 10 and 25 mg are shown as below. Brensocatib plasma exposure is highly variable, although generally in the same range between adolescents and adults. However, note that the number of adolescents is limited (n = 15 in 10-mg group, n = 16 in 25-mg group) and the PK data are also only available in about half of the enrolled adults in each treatment arm. In adults, there was no apparent difference in brensocatib plasma concentrations between the Main Study and the Substudy.

Table 91. Summary of Brensocatib Plasma Concentrations Over the Treatment Period in Adults-Substudy and Main Study

	Brensocatib 10 mg						Brensocatib 25 mg					
	Substudy			Main Study[a]			Substudy			Main Study[a]		
Visit	n	Mean (CV%) (ng/mL)	Range (ng/mL)	n	Mean (CV%) (ng/mL)	Range (ng/mL)	n	Mean (CV%) (ng/mL)	Range (ng/mL)	n	Mean (CV%) (ng/mL)	Range (ng/mL)
Day 1												
0.5 hours postdose	62	34.51 (97.9)	0, 143	—	—	—	64	85.13 (103.5)	0, 347	—	—	—
2 hours postdose[a]	62	44.52 (55.0)	0, 104	18	40.52 (69.1)	0, 89.8	64	120.0 (56.2)	0, 299	24	134.9 (51.4)	0.380, 308
4-8 hours postdose	61	38.13 (52.9)	0, 99.1	—	—	—	64	108.5 (46.9)	0, 252	—	—	—
Week 4												
Predose	60	57.53 (53.4)	9.72, 181	56	52.60 (68.7)	0, 210	60	131.3 (60.2)	0, 451	63	157.4 (70.8)	0, 558
2 hours postdose[a]	59	100.3 (44.1)	19.4, 258	20	100.5 (32.8)	32.1, 172	61	286.7 (38.4)	102, 590	25	293.6 (35.1)	81.9, 558
Week 16												
Predose	61	50.24 (58.1)	0, 171	94	45.19 (55.0)	0, 125	58	138.0 (64.5)	0, 410	105	131.6 (69.0)	0, 559
Week 28												
Predose	61	50.33 (54.7)	0, 143	120	49.30 (63.9)	0, 198	59	124.6 (59.8)	0.690, 356	130	143.0 (64.6)	17.9, 655
0.5 hours postdose	56	89.75 (46.0)	0.366, 244	—	—	—	55	235.5 (53.3)	55.8, 598	—	—	—
2 hours postdose[a]	58	95.33 (35.3)	25.0, 189	40	91.79 (45.3)	14.9, 219	58	271.9 (46.0)	29.4, 578	36	323.7 (40.1)	70.9, 597
4-8 hours postdose	56	86.27 (40.7)	25.0, 236	—	—	—	53	246.4 (43.7)	33.5, 535	—	—	—
Week 40												
Predose	58	51.80 (54.4)	0, 142	164	45.71 (54.2)	0, 125	55	119.3 (51.3)	0, 276	176	136.8 (63.4)	0, 520
2 hours postdose[a]	57	93.74 (32.1)	13.9, 147	47	107.3 (45.0)	21.8, 237	56	271.2 (45.0)	27.5, 585	43	302.6 (40.7)	56.4, 684
Week 52												
Predose	52	49.93 (72.2)	0, 191	194	45.78 (61.7)	0, 180	50	131.6 (56.5)	0, 412	208	135.4 (60.3)	0, 404

Source: Table 16.2.9-1c (main study), Table 16.2.9-1d (substudy)

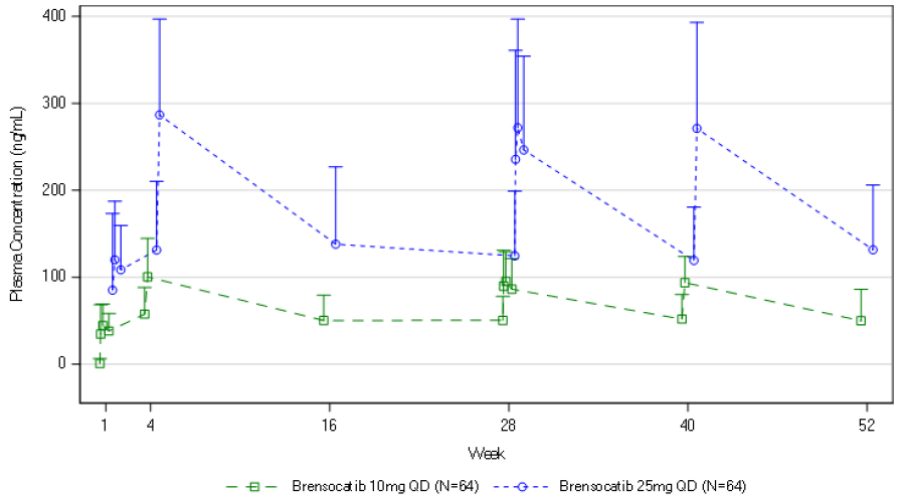
[a] For the main study, collection of PK samples from all enrolled and newly enrolled adults was implemented with Global Amendment 3. The 2-hour postdose sample was optional in the main study.

Notes: Values BLQ were set to zero. An On-Investigation Product approach was used for handling of intercurrent events.

CV% = arithmetic coefficient of variation percentage, BLQ = below limit of quantification (percentage based on number observed; LLOQ = 0.250 ng/mL), LLOQ = lower limit of quantification, n = number of participants with non-missing observations, NC = not calculated, PK = pharmacokinetic.

Source: Table 35 of Study INS1007-301 CSR

Figure 53. Mean (+SD) Brensocatib Plasma Concentrations Over Time in Adults on Linear Scale (Substudy)



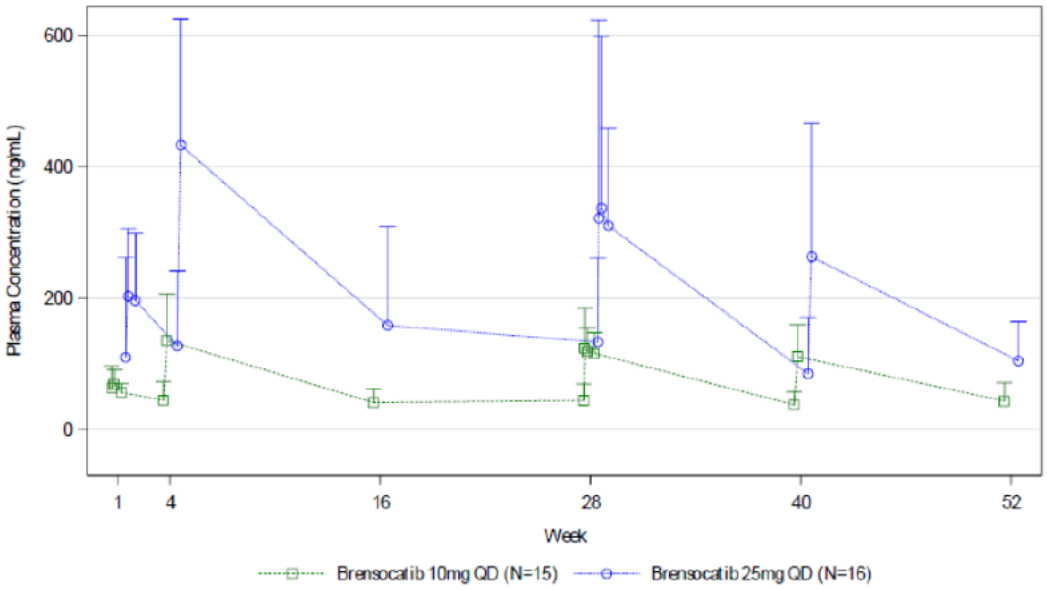
Source: Figure 16.2.9-3g (substudy)
Notes: Values BLQ were set to zero.
An On-Investigation Product approach was used for handling of intercurrent events.
Week 1 refers to the baseline assessment.
BLQ = below the limit of quantification, LLOQ = lower limit of quantification (LLOQ = 0.025 ng/mL), PK = pharmacokinetic, QD = once daily, SD = standard deviation.
Source: Figure 10 of Study INS1007-301 CSR

Figure 54. Summary of Brensocatib Plasma Concentrations Over the Treatment Period in Adolescents (Substudy)

	Brensocatib 10 mg			Brensocatib 25 mg		
Visit	n	Mean (CV%) (ng/mL)	Range (ng/mL)	n	Mean (CV%) (ng/mL)	Range (ng/mL)
Day 1						
0.5 hours postdose	12	63.20 (51.7)	18.9, 122	14	109.3 (139.1)	0, 432
2 hours postdose	13	68.33 (32.5)	31.2, 114	14	202.5 (50.7)	31.7, 395
4-8 hours postdose	12	56.07 (24.1)	33.8, 80.7	14	196.1 (52.4)	31.6, 399
Week 4						
Predose	14	44.10 (64.2)	0.590, 101	16	126.6 (90.4)	0, 439
2 hours postdose	13	134.9 (52.8)	53.2, 326	16	432.9 (44.3)	232, 1010
Week 16						
Predose	14	40.62 (51.6)	0, 71.8	15	158.1 (95.7)	0, 461
Week 28						
Predose	14	43.74 (57.2)	0, 91.4	11	132.9 (96.3)	0, 337
0.5 hours postdose	11	123.4 (49.1)	37.9, 245	10	321.6 (93.8)	0, 889
2 hours postdose	13	118.5 (30.5)	60.2, 206	10	336.9 (77.7)	0.690, 748
4-8 hours postdose	11	115.4 (27.7)	66.0, 184	10	309.9 (48.0)	0.965, 541
Week 40						
Predose	10	37.30 (52.5)	0, 57.5	7	84.39 (102.3)	0, 218
2 hours postdose	10	110.4 (43.9)	41.9, 215	7	262.8 (77.6)	1.09, 520
Week 52						
Predose	6	43.02 (64.8)	0, 70.7	7	104.0 (57.8)	0, 191

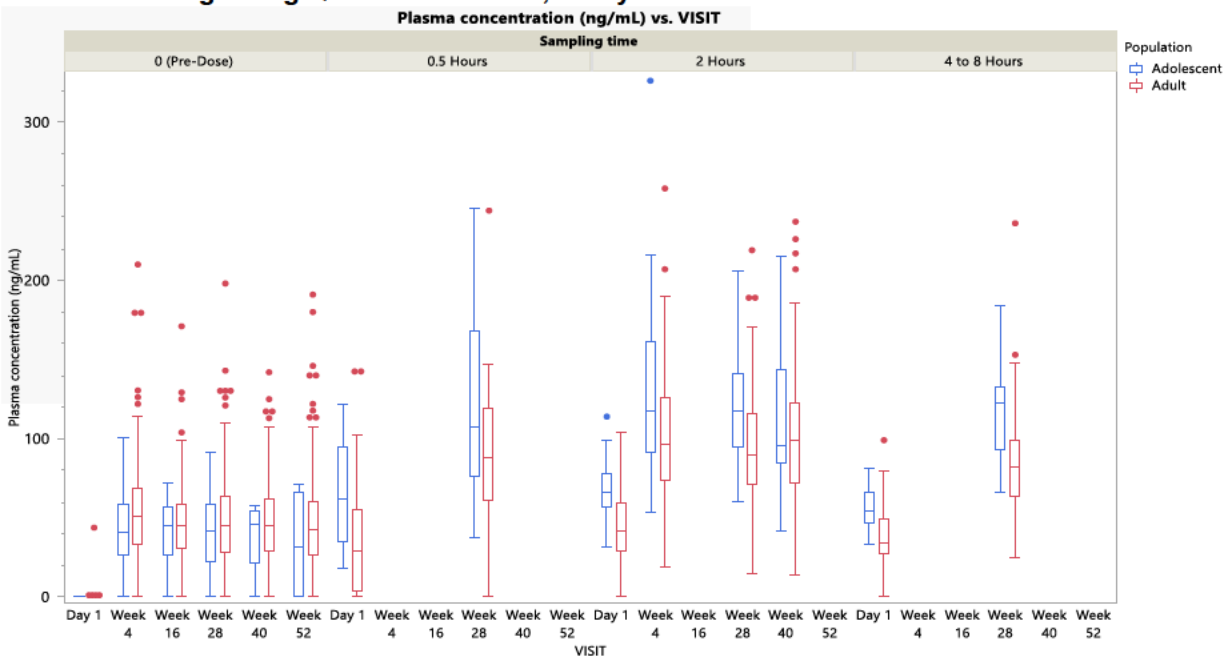
Source: Table 16.2.9-1b
Notes: Values BLQ are set to zero. An On-Investigation Product approach was used for handling of intercurrent events.
%CV = arithmetic coefficient of variation percentage, BLQ = below limit of quantification (percentage based on number observed; LLOQ = 0.250 ng/mL), LLOQ = lower limit of quantification, n = number of participants with non-missing observations, NC = not calculated, PK = pharmacokinetic.
Source: Table 36 of Study INS1007-301 CSR

Figure 55. Mean (+SD) Brensocatib Plasma Concentrations Over Time in Adolescents on Linear Scale (Substudy)



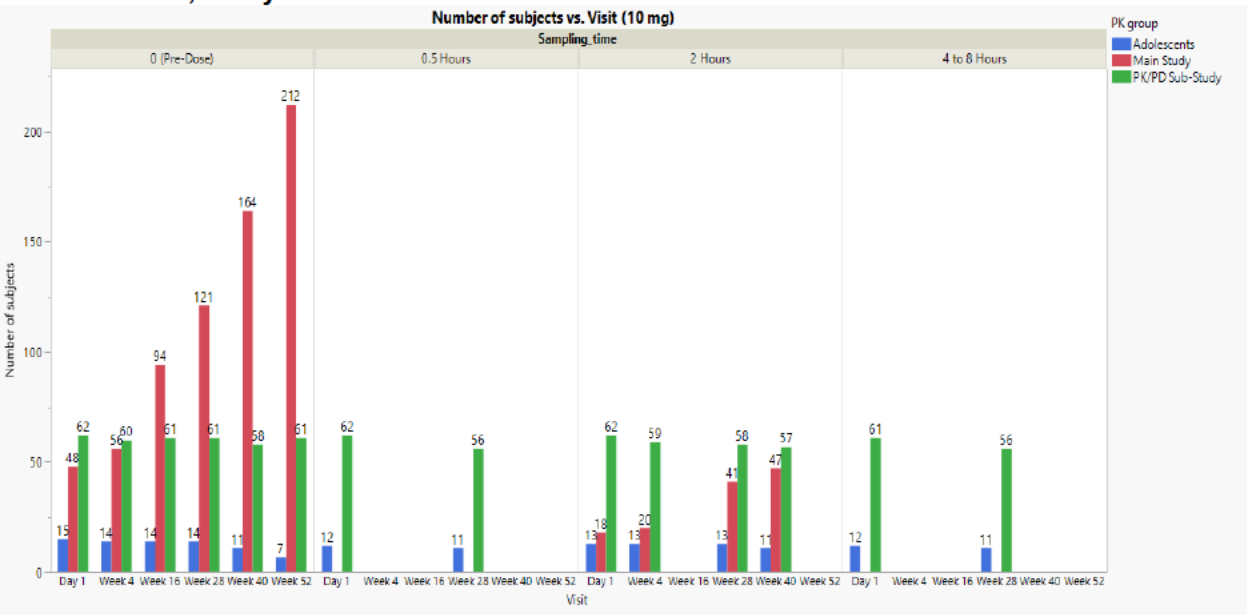
Source: Figure 16.2.9-3c
Notes: Values BLQ were set to zero.
An On-Investigation Product approach was used for handling of intercurrent events.
Week 1 refers to the baseline assessment.
BLQ = below the limit of quantification, LLOQ = lower limit of quantification (LLOQ = 0.025 ng/mL), PK = pharmacokinetic, QD = once daily, SD = standard deviation.
Source: Figure 11 of Study INS1007-301 CSR

Figure 56. Boxplot of Brensocatib Plasma Concentrations by Sampling Time in Adolescents and Adults Following 10 mg QD Administration, Study 301



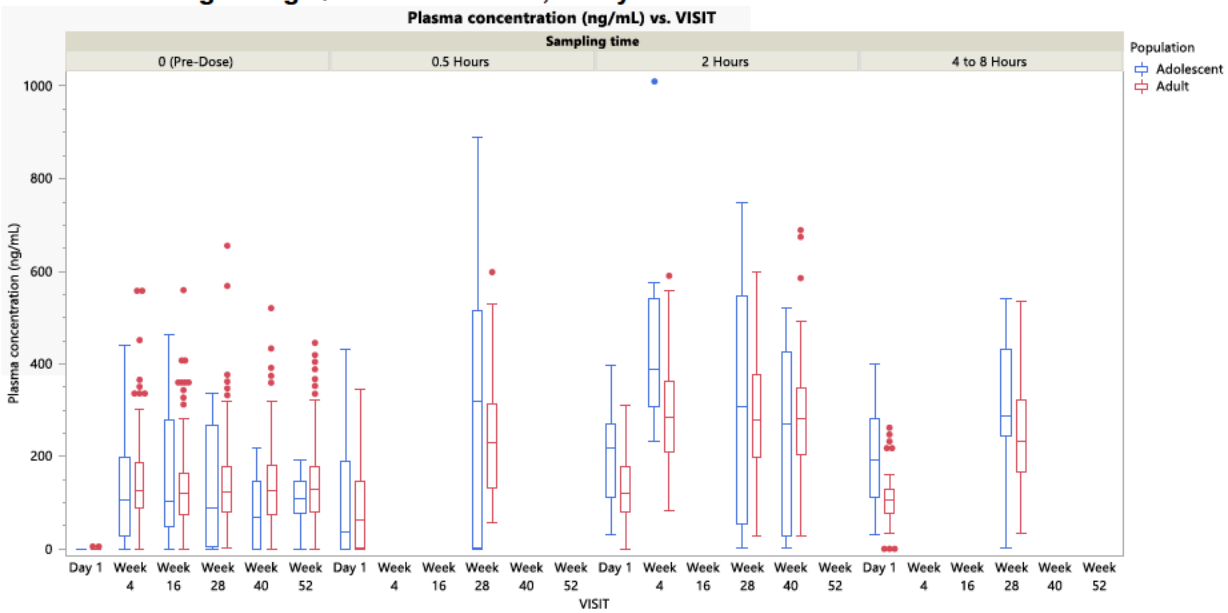
Source: FDA analysis
Abbreviation: QD, once daily

Figure 57. Summary of the Number of Adolescents and Adults Following 10 mg QD Administration, Study 301



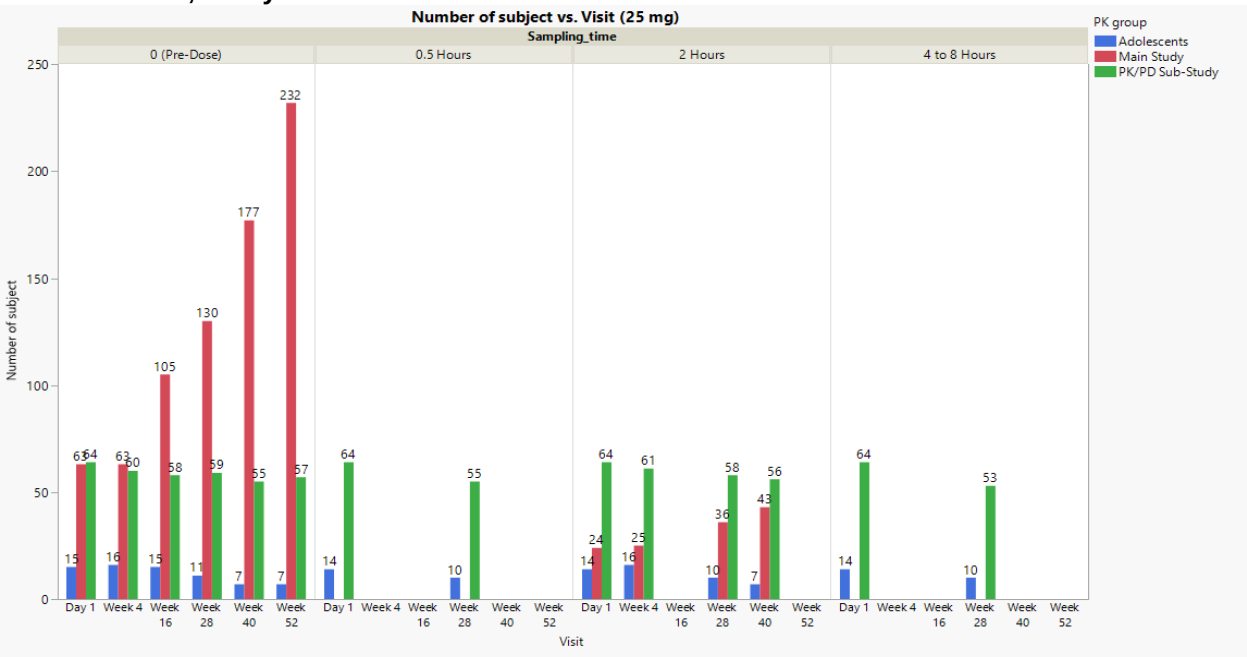
Source: FDA analysis
Abbreviation: QD, once daily

Figure 58. Boxplot of Brensocatib Plasma Concentrations by Sampling Time in Adolescents and Adults Following 25 mg QD Administration, Study 301



Source: FDA analysis
Abbreviation: QD, once daily

Figure 59. Summary of the Number of Adolescents and Adults Following 25 mg QD Administration, Study 301



Source: FDA analysis
Abbreviation: QD, once daily

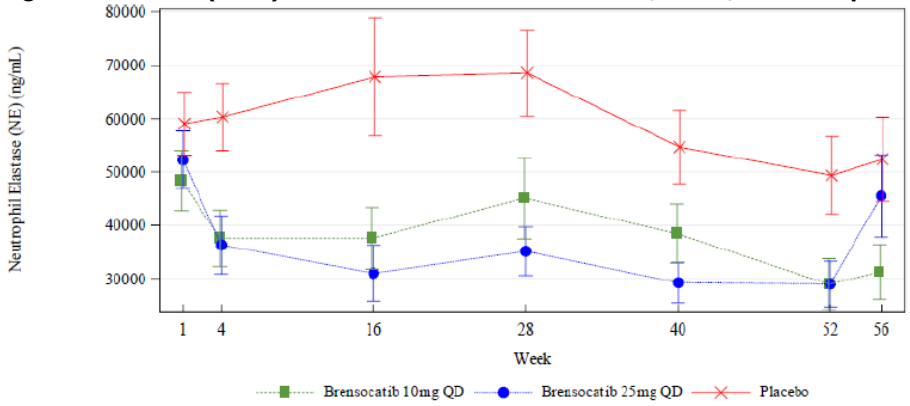
INS1007 Metabolite Thiocyanate (M8) PK Results

Thiocyanate plasma concentrations from 22 subjects with possible metabolite toxicity events were analyzed using 43 available PK samples. Among those with a possible metabolite toxicity event, thiocyanate plasma concentrations ranged from 0.339 to 8.53µg/mL. The highest thiocyanate concentration of 8.53 µg/mL was at Week 28 in one participant in the placebo group who had no baseline measurement. All postdose thiocyanate concentrations were similar to baseline. Thus, no correlation was observed between thiocyanate concentrations and possible metabolite toxicity events.

PD Results

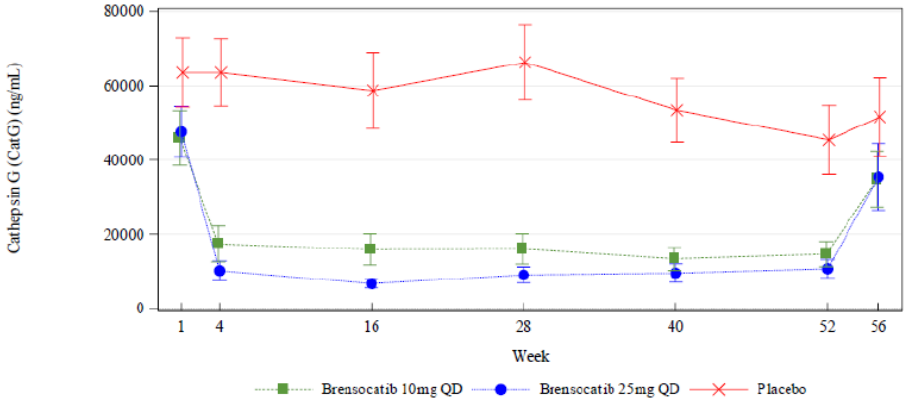
The effect of brensocatib on NSPs (NE, CatG, PR3) in sputum and blood over the 52-week treatment and 4-week follow-up periods were evaluated as exploratory objectives. Overall, the concentrations of active NSPs (also referred to as NSP activity) in sputum and blood were highly variable. Compared to placebo, brensocatib treatment reduced NSP activity in sputum, but not in blood. In sputum, the reduction in NSP activity was dose-dependent.

Figure 60. Mean (± SE) Concentrations of Active NE, CatG, PR3 in Sputum of Adults



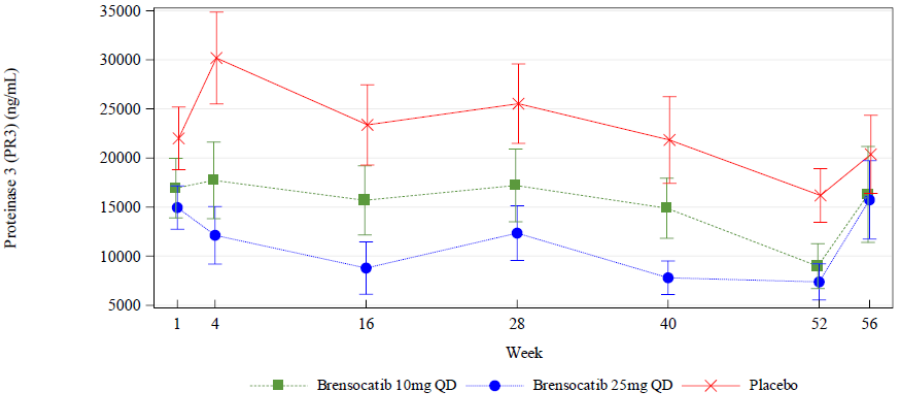
Number of Participants with Observation

Brensocatib 10mg QD	105	96	97	92	88	81	69
Brensocatib 25mg QD	108	96	98	95	87	85	67
Placebo	115	102	102	104	100	83	77



Number of Participants with Observation

Brensocatib 10mg QD	105	95	97	92	88	81	69
Brensocatib 25mg QD	108	96	98	95	87	84	67
Placebo	115	102	102	104	100	83	77

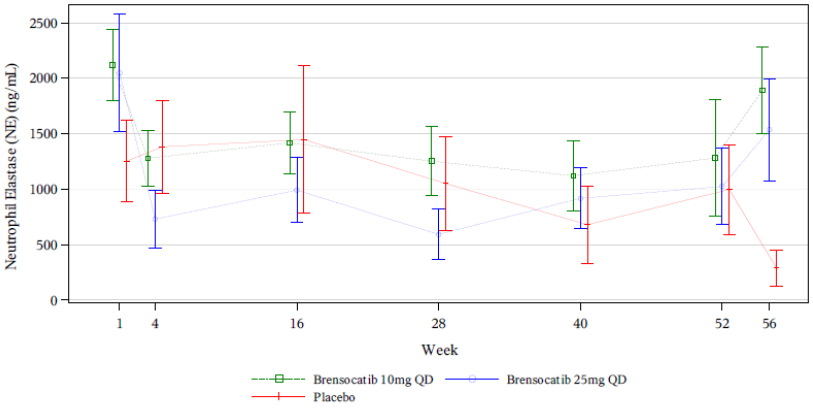


Number of Participants with Observation

Brensocatib 10mg QD	105	96	97	91	88	81	69
Brensocatib 25mg QD	108	96	97	95	87	85	67
Placebo	115	102	102	104	100	83	77

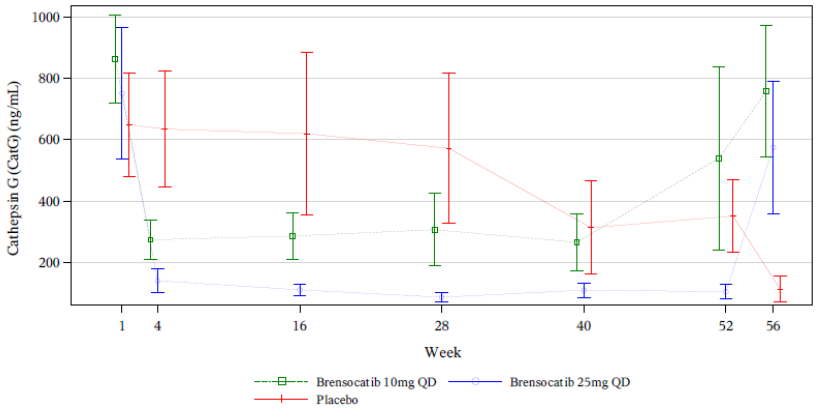
Source: Figures 12, 13, 14 of Study INS1007-301 CSR
Pretreatment (baseline) at Week 1 was the arithmetic mean value of pharmacodynamic parameter results at Screening and Day 1.
Abbreviations: CatG, Cathepsin G; NE, neutrophil elastase; PR3, proteinase 3; QD, once daily

Figure 61. Mean (± SE) Concentrations of Active NE, CatG, PR3 in Blood of Adults



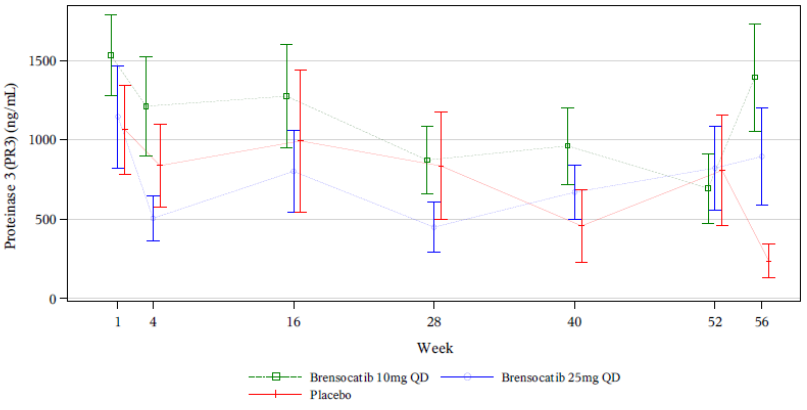
Number of Participants with Observation

Brensocatib 10mg QD	15	15	15	15	15	12	14
Brensocatib 25mg QD	12	12	12	9	10	7	9
Placebo	9	9	7	6	8	8	8



Number of Participants with Observation

Brensocatib 10mg QD	15	15	15	15	15	12	14
Brensocatib 25mg QD	12	12	12	9	10	7	9
Placebo	9	9	7	6	8	8	8



Number of Participants with Observation

Brensocatib 10mg QD	15	15	15	15	15	12	14
Brensocatib 25mg QD	12	12	12	9	10	7	9
Placebo	9	9	7	6	8	8	8

Source: Figures 16.2.10.2-2a, 16.2.10.2-2b, 16.2.10.2-2c of Study INS1007-301 CSR
Abbreviations: CatG, Cathepsin G; NE, neutrophil elastase; PR3, proteinase 3; QD, once daily

14.3. Bioanalytical Method Validation and Performance

Quantification of Brensocatib in Human Plasma

Concentrations of brensocatib in human plasma samples have been measured using adequately validated high performance liquid chromatographic separation with tandem mass spectrometric assays in clinical pharmacology studies. All clinical samples were analyzed within the established stability periods.

Table 92. Bioanalytical Methods for Quantification of Brensocatib (INS1007/AZD7986) in Human Plasma

Method	Method Validation TP70436	Method Validation AZD7HPP	Method Validation BRENHPP
Reports	VISMN1700P1	8309775	8462136
Validation	Full validation	Full validation	Transferred from method AZD7HPP and cross-validation
Platform	LC-MS/MS	LC-MS/MS	LC-MS/MS
LLOQ-ULOQ	0.250 to 150 ng/mL	0.841 to 841 ng/mL	0.841 to 841 ng/mL
Clinical studies	INS1007-101 INS1007-102 INS1007-201 INS1007-301	D6190C00001 D6190C00003	INS1007-103 INS1007-104 INS1007-105 INS1007-106 INS1007-109

Source: FDA summary
Abbreviations: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification

Table 93. Summary of Method Validation Performance (Report VISMN1700P1)

Bioanalytical method validation report name, amendments, and hyperlinks	Determination of INS1007 in Human Plasma, with K_2EDTA as Anticoagulant, by LC-MS/MS Report VISMN1700P1 Report VISMN1700P1 Amendment 1 Report VISMN1700P1 Amendment 2
Method description	In this method, INS1007 and internal standard INS1007$^{13}C_6$, were extracted from human plasma using liquid-liquid extraction. After extraction, the residue was chromatographed using reversed phase HPLC with a Pursuit C18 analytical column. INS1007 and INS1007$^{13}C_6$ were detected by monitoring the precursor and product ions (m/z 421.2→100.1 for INS1007 and m/z 427.2→100.1 for INS1007$^{13}C_6$) using an Applied Biosystems Sciex API5000 or API5500 LC-MS/MS. The quantitation was based on setting a calibration graph using the internal standard.
Materials used for standard calibration curve and concentration	Calibration curve: 0.250 (LLOQ), 0.500, 6.00, 15.0, 30.0, 60.0, 120, and 150 (ULOQ) ng/mL of Reference Standard INS1007 in human plasma.
Validated assay range	0.250 to 150 ng/mL
Material used for QCs and concentration	Quality Controls: 0.250 (LLOQ), 0.750, 45.0, 113 ng/mL of Reference Standard INS1007 in human plasma.
MRDs	NA
Source and lot of reagents	Reference Standard INS1007: Lot L004509 [redacted] (b) (4) expiration/retest: 07 APR 2018; Lot L004509 [redacted] expiration/retest: 30 NOV 2018 Internal Standard INS1007$^{13}C_6$:
	Lot AZ13661059-019 [redacted] (b) (4) expiration/retest: 28 JUN 2019 Matrix: K_2EDTA Human Plasma Combo-5-45-1, Lot numbers: R312463 (Biochemed), BRH1183340 (Bioreclamation), BRH1183342 (Bioreclamation); K_2EDTA Human Plasma BC244951D-1, Lot number: BC244951D-1 (Biochemed); K_2EDTA Human Plasma Combo-5-160-1, Lot numbers: BC25149EK-2 (Biochemed), BC25149EK-3 (Biochemed)
Regression model and weighting	linear regression: $y = a + bx$; weighting: $1/x^2$

Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Report VISMN1700P1 [Table 12]
	Cumulative accuracy (%bias) from LLOQ to ULOQ - INS1007	-1.7 to 1.7 % bias	Report VISMN1700P1 [Table 12]
	Cumulative precision (CV%) from LLOQ to ULOQ - INS1007	≤ 3.9 % CV	Report VISMN1700P1 [Table 12]
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	Intra-assay: -4.0 to 2.4% bias (LLOQ); -4.1 to 0.8% bias (above LLOQ)	Report VISMN1700P1 [Table 13]
	QCs for INS1007: 0.250 (LLOQ), 0.750, 45.0, 113 ng/mL	Inter-assay: -1.4% bias (LLOQ); -2.7 to 0.3% bias (above LLOQ)	Report VISMN1700P1 [Table 14]
	Inter-batch CV% QCs for INS1007: 0.250 (LLOQ), 0.750, 45.0, 113 ng/mL	Intra-assay: 4.5 to 6.2% CV (LLOQ); 1.4 to 7.3% CV (above LLOQ) Inter-assay: 5.9% CV (LLOQ); 2.0 to 5.7% CV (above LLOQ)	Report VISMN1700P1 [Table 13] Report VISMN1700P1 [Table 14]
Selectivity & matrix effect	No matrix effect observed during original validation based on matrix factor assessment in K_2EDTA plasma from healthy donors (6 spiked matrix lots). No matrix effect observed for LQC and HQC in K_2EDTA plasma from healthy donors (6 spiked matrix lots). No matrix effect observed for HQC in K_2EDTA plasma from subjects with renal impairment. Minor matrix effects (%bias 10.7 to 21.6%) were observed at the LQC level in K_2EDTA plasma from subjects with renal impairment.		Report VISMN1700P1 [Table 7], [Table 8]; Report VISMN1700P1 Amendment 2 [Table 8], [Table 9]

Interference & specificity	Matrix lots free of interference at the retention times of the analytes of interest.	Report VISMN1700P1 [Section 9.3.1]
Hemolysis effect	No hemolysis effect observed.	Report VISMN1700P1 [Table 9]
Lipemic effect	No lipemic effect observed.	Report VISMN1700P1 [Table 10]
Dilution linearity & hook effect	Accuracy of dilution demonstrated for dilution factors 2x (dilution QC = 113 ng/mL), 5x (dilution QC = 600 ng/mL), and 10x (dilution QC = 600 ng/mL).	Report VISMN1700P1 [Table 15]; Report VISMN1700P1 Amendment 2 [Table 14]
Bench-top/process stability	Bench-top stability demonstrated for 24.25 hours. Re-injection reproducibility and stability demonstrated for 2 days and 21 hours. Solution stability was assessed using internal standard INS1007-$^{13}C_6$, which is a stable-label analog of INS1007 and therefore stability is considered to be equivalent. INS1007-$^{13}C_6$ in methanol stored in glass containers (2000 ng/mL) at refrigerated temperature (2 to 8°C) is stable for up to 176 days. INS1007-$^{13}C_6$ in 25/75 methanol/LC-MS grade water stored in glass containers (4.0 ng/mL) at refrigerated temperature (2 to 8°C) is stable for up to 176 days.	Report VISMN1700P1 [Table 17], [Table 23]; Report VISMN1700P1 Amendment 2 [Table 15], [Table 16]
Freeze-Thaw stability	Freeze-thaw stability demonstrated for 4 cycles at -20°C/RT and -70°C/RT.	Report VISMN1700P1 [Table 16]
Long-term storage	Long-term stability demonstrated for 475 days at -20°C and for 1531 days at -70°C.	Report VISMN1700P1 [Table 18]; Report VISMN1700 P1 Amendment 1 [Table 8]
Parallelism	NA	NA
Carry over	Acceptance criteria for carry over were met.	Report VISMN1700P1 [Section 9.3.4]

Source: Table 21 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: APR, April; C, Celsius; CV, coefficient of variation; HPLC, high-performance liquid chromatography; HQC, high-concentration quality control; K_2EDTA, dipotassium ethylenediaminetetraacetic acid; JUN, June; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low-concentration quality control; MRDs, minimum required dilutions; NA, not applicable; NOV, November; QC, quality controls; RT, room temperature; ULOQ, upper limit of quantification

Table 94. Summary of Method Validation Performance (Report 8309775)

Bioanalytical method validation report name, amendments, and hyperlinks	AZD7986: Validation of a Method for the Determination of AZD7986 in Human Plasma Report 8309775 Report 8309775 Addendum 1		
Method description	Protein precipitation / liquid chromatography with tandem mass spectrometric detection		
Materials used for standard calibration curve and concentration	Calibration curve: 2.00 (LLOQ), 4.00, 10.0, 25.0, 100, 400, 1000, 1800, 2000 (ULOQ) nmol/L of Reference Standard AZD7986 in human plasma. (0.841 [LLOQ], 1.68, 4.20, 10.5, 42.0, 168, 420, 757, 841 [ULOQ] ng/mL)		
Validated assay range	2.00 to 2000 nmol/mL (0.841 to 841 ng/mL)		
Material used for QCs and concentration	Quality Controls: 2.00 (LLOQ), 6.00, 90.0, 1600 and 10000 (dilution QC) nmol/mL of Reference Standard AZD7986 in human plasma. (0.841 [LLOQ], 2.52, 37.8, 673, and 4205 [dilution QC] ng/mL)		
MRDs	NA		
Source and lot of reagents	Reference Standard AZD7986: Lot C600/2 (b) (4) expiration/retest: JUL 2015 Internal Standard ($^{13}C_6$)AZ13661057: Lot AZ13661057-019 (b) (4) expiration: NA (assessed on run-by-run basis)		
Regression model and weighting	linear regression: $y = a + bx$; weighting: $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Report 8309775 [Table 7.6]
	Cumulative accuracy (%bias) from LLOQ to ULOQ - AZD7986	-6.7 to 8.0 % bias	Report 8309775 [Table 7.6]
	Cumulative precision (CV%) from LLOQ to ULOQ - AZD7986	≤ 4.9 % CV	Report 8309775 [Table 7.6]

Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for AZD7986: 2.00 (LLOQ), 6.00, 90.0, 1600 nmol/L (0.841 [LLOQ], 2.52, 37.8, 673 ng/mL)	Intra-assay: -8.0 to -6.5% bias (LLOQ); -5.6 to 3.3% bias (above LLOQ) Inter-assay: -7.5% (LLOQ); -3.8 to 1.0% (above LLOQ)	Report 8309775 [Table 7.8]
	Inter-batch %CV QCs for AZD7986: 2.00 (LLOQ), 6.00, 90.0, 1600 nmol/L (0.841 [LLOQ], 2.52, 37.8, 673 ng/mL)	Intra-assay: 4.6 to 8.4% CV (LLOQ); 1.0 to 5.3% CV (above LLOQ) Inter-assay: 6.2% CV (LLOQ); 2.5 to 4.1% CV (above LLOQ)	Report 8309775 [Table 7.8]
Selectivity & matrix effect	Acceptable selectivity demonstrated (6 spiked matrix lots).		Report 8309775 [Table 7.2]
Interference & specificity	No interference detected at the retention times of AZD7986 or the internal standard (6 blank matrix lots).		Report 8309775 [Section 4.3]
Hemolysis effect	No hemolysis effect observed.		Report 8309775 [Table 7.25]
Lipemic effect	No lipemic effect observed.		Report 8309775 [Table 7.26]
Dilution linearity & hook effect	Acceptability demonstrated for 10-fold dilution prior to analysis (dilution QC = 10000 nmol/L).		Report 8309775 [Table 7.8]
Bench-top/process stability	Stability of primary standard solutions (10000 nmol/L) demonstrated for 24 hours at RT and 35 days refrigerated. Stability of intermediate solutions (40 nmol/L) demonstrated for 24 hours at RT and 14 days refrigerated. RT matrix stability demonstrated for 24 hours. Processed sample stability demonstrated for 144 hours refrigerated.		Report 8309775 [Table 7.11], [Table 7.12], [Table 7.13], [Table 7.14], [Table 7.15], [Table 7.16], [Table 7.17], [Table 7.22]
Freeze-Thaw stability	Freeze-thaw stability demonstrated for 4 cycles at nominal -20°C/RT and nominal -80°C/RT.		Report 8309775 [Tables 7.20], [Table 7.21]
Long-term storage	Long-term stability demonstrated for 386 days at nominal -20°C and nominal -80°C.		Report 8309775 Addendum 1 [Table 6.5], [Table 6.6]
Parallelism	NA		NA
Carry over	No evidence of carry over observed.		Report 8309775 [Section 4.5]

Source: Table 20 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: C, Celsius; CV, coefficient of variation; HPLC, high-performance liquid chromatography; HQC, high-concentration quality control; K_2EDTA, dipotassium ethylenediaminetetraacetic acid; JUL, July; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low-concentration quality control; MRD, minimal residual disease; NA, not applicable; QC, quality controls; RT, room temperature; ULOQ, upper limit of quantification

Table 95. Summary of Method Validation Performance (Report 8462136)

Bioanalytical method validation report name, amendments, and hyperlinks	Method Transfer and Cross-Validation for the Determination of Brensocatib in Human Plasma by HPLC with MS/MS Detection Report 8462136 Report 8462136 Addendum 1 Report 8462136 Addendum 2
Method description	Protein precipitation / liquid chromatography with tandem mass spectrometric detection
Materials used for standard calibration curve and concentration	Calibration curve: 0.841 (LLOQ), 1.68, 4.20, 10.5, 42.0, 168, 420, 757, 841 (ULOQ) ng/mL of Reference Standard INS1007 in human plasma.
Validated assay range	0.841 to 841 ng/mL
Material used for QCs and concentration	Quality Controls: 0.841 (LLOQ), 2.52, 37.8, and 673 ng/mL of Reference Standard INS1007 in human plasma.
MRDs	NA
Source and lot of reagents	Reference Standard INS1007: Lot 19-401 (b) (4) expiration/retest: 09 DEC 2021 Internal Standard INS1007$^{13}C_6$: Lot 12232020 (b) (4) expiration/retest: 13 MAY 2022
Regression model and weighting	linear regression: y = a + bx; weighting: $1/x^2$

Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Report 8462136 [Table 6.2]
	Cumulative accuracy (%bias) from LLOQ to ULOQ - INS1007	-4.6 to 8.1 % bias	Report 8462136 [Table 6.2]
	Cumulative precision (CV%) from LLOQ to ULOQ - INS1007	NA	NA
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for INS1007: 0.841 (LLOQ), 2.52, 37.8, and 673 ng/mL	Intra-assay: -2.0% bias (LLOQ); -4.5 to 2.1% bias (above LLOQ)	Report 8462136 [Table 6.4]
	Inter-batch CV% QCs for INS1007: 0.841 (LLOQ), 2.52, 37.8, and 673 ng/mL	Intra-assay: 5.1% CV (LLOQ); 2.1 to 4.7% CV (above LLOQ)	Report 8462136 [Table 6.4]
Selectivity & matrix effect	Acceptable selectivity demonstrated for the quantification of AZD7986 and ($^{13}C_6$)AZ13661057 in Report 8309775 (6 spiked matrix lots).		Report 8309775 [Table 7.2];

	No matrix effect observed during original validation based on matrix factor assessment in K_2EDTA plasma from healthy donors (6 spiked matrix lots). No matrix effect observed for LQC and HQC in K_2EDTA plasma from healthy donors (6 spiked matrix lots) or K_2EDTA plasma from subjects with hepatic impairment.	Report 8309775 [Table 7.3], [Table 7.4]; Report 8462136 Addendum 2 [Table 6.9], [Table 6.12]
Interference & specificity	No interference detected at the retention times of AZD7986 or the internal standard (6 blank matrix lots, demonstrated in Report 8309775). Specificity demonstrated in presence of 2500 ng/mL verapamil, 5000 ng/mL itraconazole, and 5000 ng/mL hydroxy-itraconazole for blank matrix and INS1007 at LQC level (2.52 ng/mL). Specificity demonstrated in presence of 30000 ng/mL refampin, 5000 ng/mL esomeprazole, and/or 10000 ng/mL clarithromycin for blank matrix and INS1007 at LQC level (2.52 ng/mL).	Report 8309775 [Section 4.3]; Report 8462136 Addendum 1 [Table 6.5]; Report 8462136 Addendum 2 [Table 6.5], [Table 6.6], [Table 6.7], [Table 6.8]
Hemolysis effect	No hemolysis effect observed (demonstrated in Report 8309775 and confirmed in Report 8462136).	Report 8309775 [Table 7.25]; Report 8462136 Addendum 2 [Table 6.10]
Lipemic effect	No lipemic effect observed (demonstrated in Report 8309775 and confirmed in Report 8462136).	Report 8309775 [Table 7.26];
		Report 8462136 Addendum 2 [Table 6.11]
Dilution linearity & hook effect	Acceptability demonstrated in Report 8309775 for 10-fold dilution prior to analysis (dilution QC = 10000 nmol/L). In Report 8462136, acceptability of 2-fold dilutions (dilution QC = 673 ng/mL) was demonstrated and 10-fold dilutions (Dilution QC = 4210 ng/mL) were confirmed.	Report 8309775 [Table 7.8]; Report 8462136 Addendum 2 [Table 6.4]
Bench-top/process stability	Stability of internal standard working solutions (170 ng/mL) prepared in Acetonitrile demonstrated for 24 hours at RT. Re-injection reproducibility and stability demonstrated for 138 hours at 2 to 8°C.	Report 8462136 [Table 6.6]; Report 8462136 Addendum 2 [Table 6.13], [Table 6.16]
Freeze-Thaw stability	Freeze-thaw stability demonstrated at LQC and HQC level in Report 8309775 for 4 cycles at nominal -20°C/RT and nominal -80°C/RT and confirmed at Dilution QC level (4210 ng/mL) in Report 8462136 for 4 cycles at nominal -20°C/RT and nominal -70°C/RT.	Report 8309775 [Tables 7.20], [Table 7.21]; Report 8462136 Addendum 2 [Table 6.14]
Long-term storage	Long-term stability demonstrated for 386 days at nominal -20°C and nominal -80°C in Report 8309775 and confirmed at Dilution QC level (4210 ng/mL) in Report 8462136.	Report 8309775 Addendum 1 [Tables 6.5], [Table 6.6];

Carry over	No evidence of carry over observed.	Report 8462136 [Section 4.7]

Source: Table 22 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: C, Celsius; CV, coefficient of variation; DEC, December; HPLC, high-performance liquid chromatography; HQC, high-concentration quality control; K_2EDTA, dipotassium ethylenediaminetetraacetic acid; MRD, minimal residual disease; MS/MS, tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low-concentration quality control; NA, not applicable; QC, quality controls; RT, room temperature; ULOQ, upper limit of quantification

Quantification of Thiocyanate in Human Plasma

To quantify sodium thiocyanate (thiocyanate) in human plasma, the Applicant developed bioanalytical method 2206017 (lower limit of quantification [LLOQ]: 0.200µg/mL) to analyze samples from Studies INS1007-102, INS1007-104, INS1007-105, Study 201; and bioanalytical method V2304024 (LLOQ: 0.200µg/mL) to analyze samples from Study 301. All clinical samples were stored at −70°C before analysis. In a study from the literature, the storage stability of plasma samples containing thiocyanate has been reported for up to 24 months at −20°C (Scherer et al. 2020).

Bioanalytical method 2206017 was an exploratory method and the long-term stability was not assessed. In Studies INS1007-102, INS1007-104 and INS1007-105, all plasma samples were stored for less than 400 days before analysis, except for those collected from 1 subject in Study INS1007-102. Although samples from Study 201 were stored at −70°C for approximately 3 to 4 years before analysis, the thiocyanate plasma concentration data from this study were similar to those observed in Studies INS1007-102, INS1007-104 and INS1007-105.

Bioanalytical method V2304024 was a fully validated method. Long-term sample stability was demonstrated for up to 409 days at −20°C and −70°C as of November 2024. A total of 62 thiocyanate samples from Trial 301 were tested, in which 38 samples were analyzed within 409 days. Remaining samples were stored for up to 864 days before analysis. Safety assessment for Study 301 also indicated that no correlation was observed between thiocyanate concentrations and possible metabolite toxicity events.

Quantification of NSPs (NE, PR3, and CatG) in Human Sputum and White Blood Cell Pellets

To determine the NE enzymatic activity in plasma samples from Study D6190C00001, an exploratory semiquantitative assay (SBM0129VAL) was used. The method uses a 96-well plate format and utilizes a fluorogenic substrate. Cleavage of the fluorogenic substrate by NE activity yields the reaction product 7-amino 4-methyl coumarin.

To quantify the NE enzymatic activity in human white blood cell (WBC) pellets and sputum samples from Study 201, the ProteaseTag® Active Neutrophil Elastase Immunoassay kit (Cat. No. PA001, ProAxsis), a colorimetric ligand binding assay, was originally used at (b) (4) However, sample analysis of WBC pellets at (b) (4) was discontinued due to lack of method robustness. Unprocessed WBC pellet samples were stored frozen and then analyzed for NE and PR3 by the Applicant using an exploratory extraction method and exploratory kinetic enzyme assays. Samples from Study 201 were not analyzed for CatG as no method was available at the time.

To determine the NE,PR3, and CatG enzymatic activity in WBC pellets and sputum samples from Study 301, enzymatic assays (WBC: CL-VAR-030 for NE, CL-VAR-031 for PR3, and CL-VAR-029 for CatG; Sputum: 2211009 for NE, 2303015 for PR3, and 2303055 for CatG) using an exogenous peptide substrate were validated.

To determine the active NE, PR3 and CatG in sputum samples from Study 301, fluorescence-based kinetic enzyme assays (2211009 for NE, 2303015 for PR3, and 2303055 for CatG) were used. However, the stability assessments for these assays are still ongoing to cover the storage duration of clinical samples.

Overall, enzyme activity assays for the determination of enzymatic activity of NE, PR3, and CatG is considered exploratory.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Population PK Analysis

Executive Summary

FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting the analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 96. Summary of Population PK Analyses

Parameters		Information
Objectives of PPK analysis		Characterize brensocatib PK profile Identify sources of PK variability Predict individual exposure for E-R assessment
Study included		Studies D6190C00001, D6190C00003, INS1007-101, INS1007-102, INS1007-104, INS1007- 105, INS1007-106, INS1007-109, INS1007-201, (b) (4) and INS1007-301
Dose(s) included		5-120 mg single dose and 10-40 mg QD
Population included		Total of 1098; Healthy (n=291), NCFB (n=783), CF (n=24)
Population characteristics (Report ICPD 00694-1 [Table 5] and [Table 6])	General	Age [median (range)]: 59.0 (12 - 85) yr (38.8% subjects >=65 yr, 11.6% subjects >=75 yr) Weight [median (range)]: 69.7 kg (31.7 - 155 kg) Sex: 490 males (44.6%) Race: White-788 (71.8%) Asian-127 (11.6%) Other/Multiple/Unknown/Not Reported-101 (9.2%) Black or African American-66 (6.01%) American Indian or Alaska Native-3 (1.18%) Native Hawaiian or other Pacific Islander-3 (0.273%)
	Organ impairment	Hepatic impairment study (Child-Pugh scores 5-6, 7-9, 10-12,): n=6/group (0.546%) in each category

Parameters		Information
		Renal impairment study (eGFR: 60 to <90 mL/min/1.73 m^2, 30 to <60 mL/min/1.73 m^2, 15 to <30 mL/min/1.73 m^2): n=6 mild (0.546%), 6 moderate (0.546%), and 6 severe (0.546%) Renal function (CLcr, median (range)) in pooled healthy, NCFB and CF populations (n=1098): 83.7 (12.9-204) mL/min/1.73 m2
	Pediatrics (if any)	Adolescents (≥12 - <18 years): 31 of 1098 subjects in the PPK dataset (2.8%) Median Age of the adolescent group:15 years Adolescent weight median (range): 50.0 kg (31.7-85.0 kg)
No. of patients, PK samples, and BLQ (Report ICPD 00694-1 [Table 4])		Total of 783 NCFB patients were included in PPK analysis (157 from INS1007-201 with 563 PK records and 626 patients with 3337 PK records from INS1007-301). All BLQ samples (n=1064 of 17,063 observations in source data) were excluded. A total of 1064 observations labeled as BLQ were present in the source data; this included 659 samples drawn prior to the first dose of brensocatib, 102 samples drawn after a washout in a multipart Phase 1 study, and 24 samples that would otherwise have been excluded for other reasons (missing dosing information or all samples BLQ). Thus, only 279 "useable" post-dose samples were excluded from the analysis, which is only 2.3% of the concentration records in the population PK dataset.
Sampling schedule (Report ICPD 00694-1 [Table 4]))	Rich sampling	Rich PK samples were collected from all Phase 1 studies: D6190C00001, D6190C00003, INS1007-101, INS1007-102, INS1007-104, INS1007-105, INS1007-106 and INS1007-109 and from (b) (4) Detailed sampling schedules are summarized in Table 4.
	In ITT population	PK sampling schedule for INS1007-201 and INS1007-301 can be found in Table 4.
Covariates evaluated	Static	PK covariates evaluated in ICPD-00694-1 [Table 1] included Age (yr), Weight (kg), Height (cm), BSA (m^2), IBW (kg), BMI (kg/m^2), ALB (g/dL), CLcr (mL/min/1.73 m^2), Dose (mg), Renal/Hepatic Impairment, Formulation, Food Effect, CYP3A4 inhibitor/inducer, Pgp inhibitor, Sex, Race, Country of Origin, Indication/Study Phase
	Time-varying	Not applicable.

Source: Table 1 and Table 2 in IR response dated February 4, 2025.
Abbreviations: ALB, albumin; BLQ, below limit of quantification; BMI, body mass index; BSA, body surface area; CF, cystic fibrosis; CLcr, creatinine clearance; eGFR, epidermal growth factor receptor; E-R, exposure-response; ITT, intent-to-treat; NCFB, non-cystic fibrosis bronchiectasis; Pgp, P-glycoprotein; PK, pharmacokinetic; PPK, population pharmacokinetics

Table 97. Summary of Population PK Analyses (continued)

Final Model	Summary	Acceptability [FDA's Comments]
Software and version	The population PK analysis was conducted using NONMEM® version 7.4.4 (ICON) Perl-speaks-NONMEM version 4.7.0 Pirana version 2.9.9	Acceptable
Estimation algorithm	NLME model using first-order conditional estimation method with η-ε interaction	Acceptable
Model structure	The final model contained an oral depot compartment with an associated dose -dependent relative bioavailability, a 3-compartment transit chain, first-order absorption described by separate Ka values for fed and fasted states to describe the absorption profile, and two systemic compartments with linear elimination to describe the overall drug disposition.	Acceptable

Final Model	Summary	Acceptability [FDA's Comments]
Model parameter estimates	Report ICPD 00694-1 [Table 9]. Also see Table 98 in this review.	Acceptable
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	Report ICPD 00694-1 [Table 10] The resampled parameter means are aligned with those estimated in the final model fit, with 95% confidence intervals consistent with the precision of the final model.	Acceptable
BLQ for parameter accuracy	This is not applicable as all BLQ samples were excluded from the population PK dataset. This is justified given that excluded BLQ observations only represent 2.3% of the available concentration observations.	Acceptable
GOF, VPC	GOF: Report ICPD 00694-1 [Figure 26] VPC: Report ICPD 00694-1 [Figure 28 and Figure 29; See also Figure 62 and Figure 63 in this review.] Describe the model fitness (Report ICPD 00694-1 [Section 4.1.2.4]): The GOF plots demonstrate the adequacy of the model fit across the pooled dataset with minimal bias as the intercept terms are all close to 0 and the slopes are approximately 1 and conditional weighted residuals (CWRES) around the line of zero. The PC-VPC plots show good agreement between median simulated plasma concentrations, indicating the model is robust in capturing the variability in the observed concentrations. Overall, this model is expected to provide robust and reliable estimates of brensocatib plasma exposure in healthy subjects and patients with CF or NCFB. The covariate relationships identified in the model are statistically significant and are estimated with acceptable precision.	Acceptable
Significant covariates and clinical relevance	The covariate relationships identified as statistically significant in the final population PK model are provided below. The impact of each covariate is provided in parentheses. Relative F: Dose (22% increase between doses of 10 and 20 mg QD); drug-drug interactions (verapamil [65.7% increase], and clarithromycin [38.8% increase]) Ka: administration in fed state (decreased Ka by 21%); oral solution administration (increased Ka by 80%) CL/F: body weight (increased CL/F with increasing weight with coefficient of 0.75); Sex (slower CL/F in females [9.6%]); Race (faster CL/F for Blacks [49.2%] and Asians [22.9%]); Child-Pugh class (18.7% increase in CL/F for each increase in class); drug-drug interactions (rifampin [38.3% increase], verapamil [21.2% increase], and clarithromycin [7.8% decrease]) Vc/F: body weight (increased Vc/F with increasing weight with coefficient of 1.0); age (increased Vc/F with increasing age with a coefficient of 0.314) Q/F: body weight (increased Q/F with increasing weight with coefficient of 0.75) Vp/F: body weight (increased Vp/F with increasing weight with coefficient of 1.0) The forest plots of simulated AUC_{24} and C_{max} for statistically significant covariates are presented in Report ICPD 00694-1 [Figure 37 and Figure 38], respectively.	Acceptable

Final Model	Summary	Acceptability [FDA's Comments]
Analysis based on simulation (optional)	As discussed above, model-based simulations were used to assess the potential clinical relevance of statistically significant covariates.	Acceptable

Source: Table 1 and Table 2 in IR response dated February 4, 2025.
Abbreviations: AUC, area under the concentration-time curve; BLQ, below limit of quantification; CF, cystic fibrosis; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CWRES, conditional weighted residuals; GOF, goodness-of-fit; IIV, interindividual variability; Ka, absorption rate constant; NCFB, non-cystic fibrosis bronchiectasis; NLME, nonlinear mixed-effects; PC-VPC, prediction-corrected visual predictive check; PK, pharmacokinetic; QD, once daily; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent central volume of distribution; VPC, visual predictive checks; Vp/F,; apparent peripheral volume of distribution

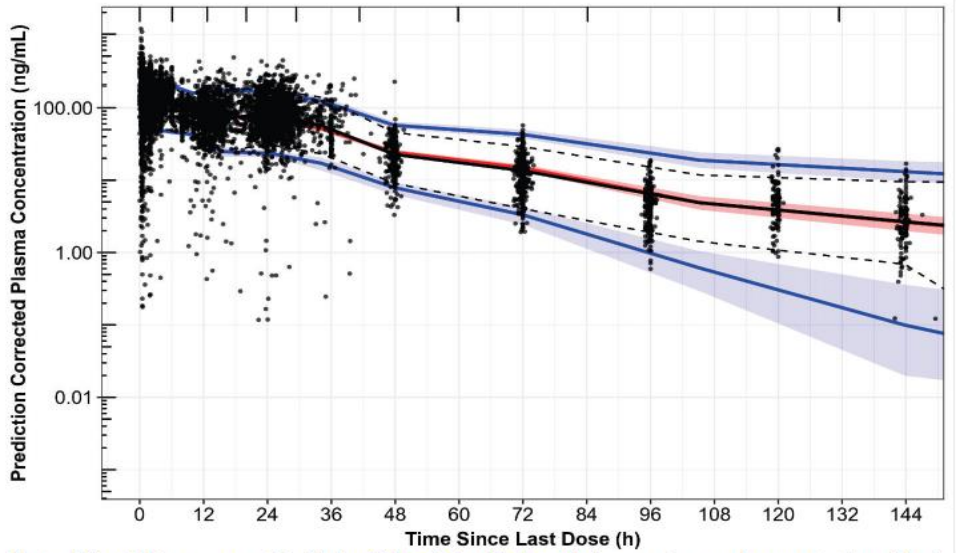
Table 98. Summary Statistics of Resampled Population PK Parameters in Comparison to the Fitted Population PK Model Parameter Estimates (Population Mean Parameters)

Parameter	Final model			Resample statistics (N = 1000)			
	Final estimate	%SEM	Shrinkage	Mean	Median	%CV	90% CI
CL/F (L/hr/70kg)[a]	3.25	0.0838	2.58	3.2	3.19	2.28	[3.08, 3.32]
CL/F-Hepatic Impairment[b]	0.187						
CL/F-Rifampin[c]	0.383						
CL/F-Clarithromycin[d]	-0.0779						
CL/F-Verapamil[e]	0.212						
CL/F-Female	-0.0957	0.0235	24.5	-0.0966	-0.0968	24.7	[-0.135, -0.0580]
CL/F-Black	0.492	0.0791	16.1	0.557	0.551	12.5	[0.448, 0.672]
CL/F-Asian	0.229	0.0442	19.3	0.216	0.219	20.1	[0.142, 0.285]
Vc/F (L/70kg)[a]	78.8	1.45	1.84	79.5	79.4	2.05	[76.9, 82.3]
Vc/F-Age	0.314	0.0312	9.94	0.27	0.269	11.3	[0.221, 0.319]
Q/F (L/hr/70kg)[a]	5.97	0.167	2.8	5.92	5.92	2.78	[5.65, 6.20]
Vp/F (L/70kg)[a]	50.4	0.87	1.72	52.9	52.9	1.76	[51.4, 54.4]
Ka-Fasted (1/hr)	7.61	0.236	3.1	7.43	7.45	3.07	[7.04, 7.79]
Ka-Fed (1/hr)	5.8	0.415	7.16	4.62	4.62	7.93	[4.02, 5.19]
Ka-Oral Solution Formulation	0.809	0.199	24.6	0.911	0.905	17.3	[0.652, 1.17]
E0	0.29	0.011	3.8	0.284	0.283	3.75	[0.267, 0.302]
Emax	0.346	0.0221	6.39	0.332	0.332	7.61	[0.291, 0.373]
EC50 (mg)	21.6	1.36	6.29	17.1	17.1	11.5	[13.9, 20.1]
H	1.54	0.0928	6.03	1.31	1.31	6.57	[1.17, 1.45]
relF-Clarithromycin[d]	0.388						
relF-Verapamil[e]	0.657						

Note: Abbreviations are provided in the Abbreviation Listing.
a. Clearance and volume parameters were allometrically scaled using fixed exponents of 0.75 and 1, respectively.
b. Entirely informed by data from Study INS1007-105.
c. Entirely informed by data from Study INS1007-106.
d. Entirely informed by data from Study INS1007-109.
e. Entirely informed by data from Study D6190C00003.

Source: Table 9 in Report ICPD 00694-1
Abbreviations: CI, confidence interval; CL/F, apparent clearance; CV, coefficient of variation; Ka, absorption rate constant; E0, baseline effect/response; EC50, half maximal effective concentration; Emax, maximum effect; N, number of subjects; relF, relative bioavailability; Q/F, apparent intercompartmental clearance; Vc/F, apparent central volume of distribution; Vp/F, apparent peripheral volume of distribution; SEM, standard error of mean

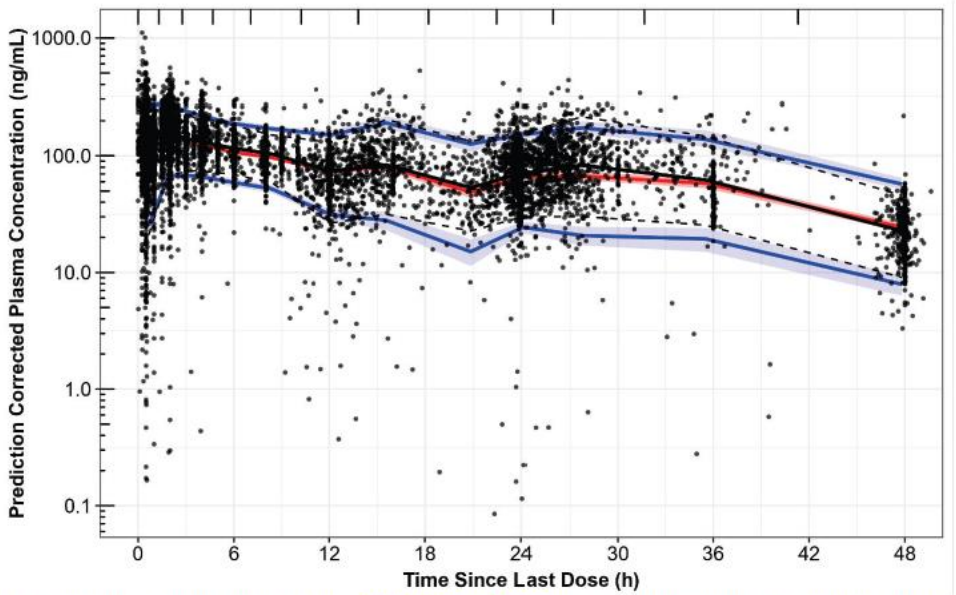
Figure 62. Prediction-Corrected Visual Predictive Check Plot for the Final Population PK Model Using the Pooled Analysis Dataset



Note: Abbreviations are provided in the Abbreviation Listing. Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Black tick marks at top of figure indicate the times since last dose at which the data were binned for the calculation of summary statistics. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations.

Source: Figure 28 in Report ICPD 00694-1.
Abbreviation: PK, pharmacokinetic

Figure 63. Prediction-Corrected Visual Predictive Check Plot for the Final Population PK Model Using the Pooled Analysis Dataset, Truncated to the First 48 Hours After a Dose



Note: Abbreviations are provided in the Abbreviation Listing. Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Black tick marks at top of figure indicate the times since last dose at which the data were binned for the calculation of summary statistics. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations.

Source: Figure 29 in Report ICPD 00694-1.
Abbreviation: PK, pharmacokinetic

14.5.1. Exposure Response (Efficacy) Executive Summary

FDA's Assessment

In general, the Applicant's exposure response analyses on efficacy are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. Significant relationships were found between brensocatib exposure (AUC_{24}) thresholds and the three efficacy outcomes that were evaluated: annualized rate of pulmonary exacerbations, time to first pulmonary exacerbation, and change from baseline in post-bronchodilator FEV1. Note that thresholds were defined above and below which significant differences in outcome were seen for all three outcomes. However, the exposure-response population only contains a subset (~50%) of the ITT population, so the exposure-response relationship for efficacy should be interpreted with caution.

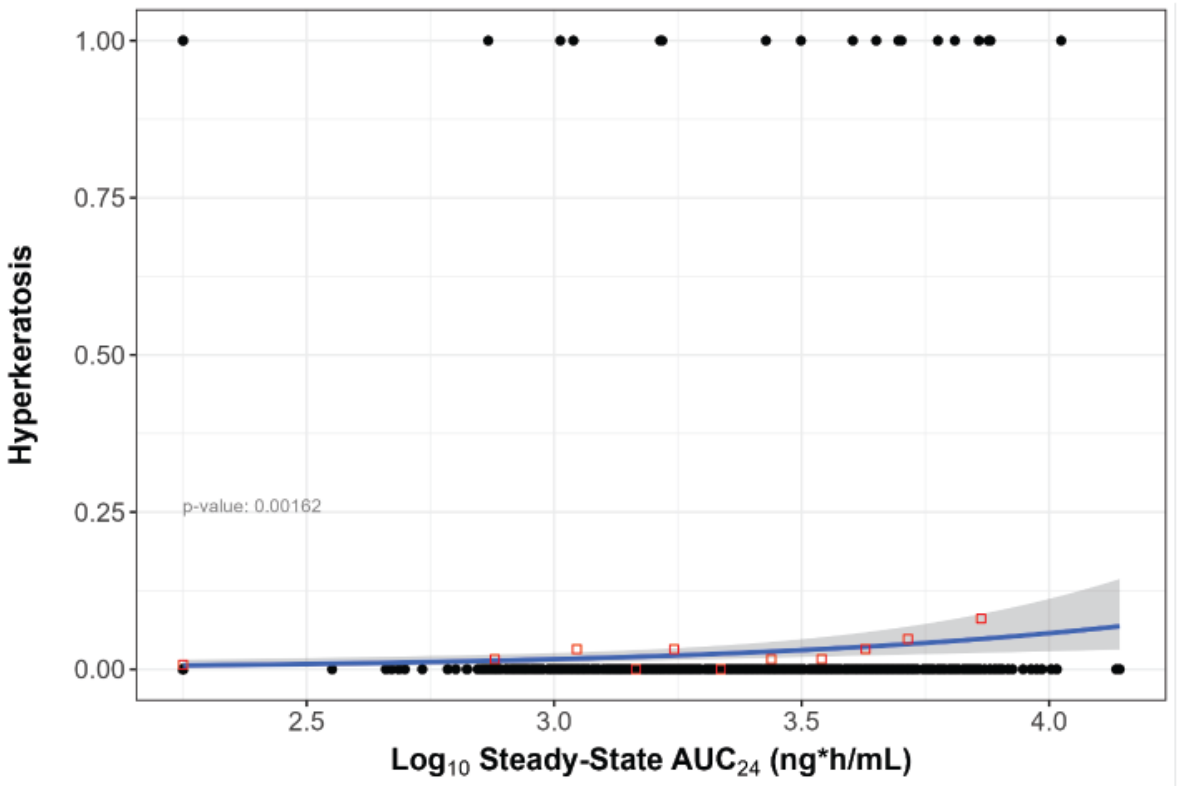
14.5.2. Exposure Response (Safety) Executive Summary

FDA's Assessment

In general, the Applicant's exposure response analyses on safety are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Using multivariable logistic regression, a statistically significant relationship was found between AUC_{24} as a continuous variable and the incidence of mild-moderate hyperkeratosis. The relationship between log10-transformed AUC_{24} and hyperkeratosis was confirmed when fitting the univariable logistic regression model to the data with placebo patients excluded (Figure 64).

Figure 64. Results of the Univariable Logistic Regression Model Exploring the Potential Relationship Between Steady-State AUC_{24} by Occurrence of Hyperkeratosis, Paneled by AESI Category and Using AUC_{24} as a Linear Continuous Variable



Note: Abbreviations are provided in the Abbreviation Listing. Solid circles at top and bottom of plot represent the individual observations with associated occurrence of AESI (0 = No, 1 = Yes). Blue line and grey shaded region are the mean (+/- 1 standard error) from the fit of a logistic regression model to the data. Red, open squares are the incidence of in bins of approximately equal size (all placebo patients binned together)

Source: Figure 52 in Report ICPD 00694-1
Abbreviations: AESI, adverse events of special interest; AUC, area under the concentration-time curve

14.5.3. Physiologically-Based Pharmacokinetic Analysis Review

Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK modeling analyses to predict the following:

- Drug-drug interaction potential of brensocatib on the exposure of a sensitive substrate of CYP3A4 (midazolam)

The Division of Pharmacometrics has reviewed the PBPK submission (Report IMD/1/B and associated modeling and simulation files) to conclude the following:

- The PBPK analysis indicated a low likelihood for a clinically relevant DDI of brensocatib (25 mg QD) with a substrate of CYP3A4.

Methods

Brensocatib PBPK Model Development

The PBPK analyses were performed using the software Simcyp® version 21.

The absorption of brensocatib was described using mechanistic absorption model (Simcyp Advanced Dissolution, Absorption, and Metabolism model). The fraction of brensocatib absorbed (fa) was estimated from mass balance data (human absorption, distribution, metabolism, and excretion study INS1007-103), which indicated almost complete drug absorption at 40-mg dose (2.4% unchanged drug in feces).

The distribution of brensocatib were described using a minimal PBPK model with single-adjustment compartment, respectively.

The elimination kinetics were used to describe the elimination of brensocatib. The estimated apparent oral clearance (CL/F) value of 5.6 L/h, following multiple oral doses of 10 to 40mg QD brensocatib to both healthy volunteers and patients, from population pharmacokinetics analysis (Report ICPD 00566-1), was used to calculate the CYP isoforms intrinsic clearance values. In vitro HLM data combined with metabolite profiling from the mass balance study were used to assign the relative contribution of the CYP isoforms CYP3A4, CYP2C8, and CYP2D6 to the clearance of brensocatib. Intestinal P-gp clearance was calculated from available in vitro permeability data. The relative contributions of CYP3A4 to the overall clearance of brensocatib (fmCYP3A4) and intestinal P-gp clearance were adjusted using the clinical DDI data with verapamil (Study D6190C00003). The reported renal clearance value of 1.53 L/h from the mass-balance study (Study INS1007-103) was used as input parameter.

Brensocatib was determined to be a CYP3A4 inducer in vitro. Brensocatib induced messenger ribonucleic acid (mRNA) for CYP3A4 in one of the three hepatocyte donors evaluated (Report 8492164). The in vitro estimated values for calibrated maximal fold induction (Ind_{max}) and inducer concentration that supports half-maximal induction (Ind_{C50}) were 1.75-fold and 3.24µM, respectively.

The inhibitory potential of brensocatib towards the CYP isoforms 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4/5 was investigated in HLM. Brensocatib did not show reversible or time-dependent inhibition of any CYP isozymes evaluated (Report ADME-AZS-Wave3-140529; ADME-AZSWave3- 140530; ADME-AZS-Wave3-140613).

The input parameters for brensocatib PBPK model are listed in Table 99.

Table 99. Input Parameters for Brensocatib PBPK Model

Parameter	Value	Reference
Physicochemical and binding parameters		
MW (g/mol)	420.465	Data Checklist/IB v5, section 3.1
Log P	-2.1	Personal correspondence
Compound type	Base	SIVA
pKa	8.1	Data Checklist
B:P	0.7	INS1007-103 (draft report)
fu	0.128	ADME-AZS-Wave4-130621
Main binding protein	Albumin	Assumed

Parameter	Value	Reference
Absorption model – ADAM model		
P_{app} (x10^{-6} cm/s)	24.22	Optimised, SIVA
Calibrator P_{app} (x10^{-6} cm/s)	Not provided	
P_{eff} (x10^{-6} cm/s)	2.64	Predicted, MechP_{eff}
$P_{trans,0}$ (x$^{10-6}$ cm/s)	1527	Calibrated against Caco-2 P_{app} data
Q_{gut} (L/h)	11.76	Predicted
fu_{gut}	1.00	Assumed
ka (h^{-1})	1.15	Predicted
fa	0.976	Calculated, human mass balance data
F_G	1	Predicted from ADAM model
Regional Abs. Scalar – J1	2.5	Optimised to improve the prediction of C_{max}
Regional Abs. Scalar – J2	2.0	
Distribution model – minimal PBPK model		
V_{ss} (L/kg)	1.24	Predicted, method 2
CL_{in} (L/h)	70.62	Optimised
CL_{out} (L/h)	51.93	Optimised
V_{SAC} (L/kg)	1.18	Optimised
Elimination parameters		
CL/F (L/h)	5.595	PopPK estimate
$fm_{h,CYP3A4}$	0.20	Optimised value (Study D6190C00003)
$f_{mh,CYP2C8}$	0.036	ADME-AZS-Wave3-140531-CYP phenotyping
$f_{mh,CYP2D6}$	0.021	
CYP3A4 CL_{int} (µL/min/pmol)	0.013	Retrograde CL calculation
CYP2C8 CL_{int} (µL/min/pmol)	0.016	
CYL2D6 CL_{int} (µL/min/pmol)	0.022	
HLM CL_{int} (µL/min/mg)	5.983	
fu_{mic}	0.9812	Human hepatocyte metabolism BE000901_12
CL_R (L/h)	1.53	Study INS1007-103
Transport parameters		
P-gp CL_{intT} (uL/min)	1.192	SIVA fitted value
RAF/REF	5	Optimised value (Study D6190C00003)
fu_{inc}	1	Default
Interaction parameters		
MATE1 K_i (µM)	5.745	Report 16AZTrPISI
MATE-2K K_i (µM)	7.65	
fu_{inc}	1	Assumed
CYP3A4 Ind_{max}	1.75	Personal correspondence; draft data from Labcorp (Study 8492164)
CYP3A4 $IndC_{50}$ (µM)	3.24	

Source: Table 5 of the PBPK report IMD/1/B
Abbreviations: ADAM, advanced dissolution, absorption and metabolism; ADME, absorption, distribution, metabolism and excretion; B:P ratio, blood to plasma ratio; Caco-2, human colon adenocarcinoma cells; CL, clearance; CL_{in}, input clearance to single adjusting compartment; CL_{out}, output clearance from single adjustment compartment; CL_R, renal clearance; CL/F, apparent oral clearance; CL_{int}, intrinsic clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450 enzyme; fa, fraction available for oral absorption from dosage form; fm_h, fraction of hepatic metabolism; F_G, intestinal availability; fu, fraction unbound in plasma; fu_{gut}, fraction unbound in enterocytes (gut); fu_{inc}, fraction of drug unbound in hepatocyte incubation; fu_{mic}, free fraction of drug in an in vitro microsomal preparation; HLM, human liver microsomes; Ind_{C50}, inducer concentration that supports half maximal induction; Ind_{max}, maximal fold induction over vehicle; Ka, absorption rate constant; K_i, inhibition constant; logP, logP octanol:water partition coefficient; MATE1, multidrug and toxin extrusion protein 1; MATE-2K, multidrug and toxin extrusion protein 2; MW, molecular weight; P_{app}, apparent permeability coefficient; P_{eff}, effective permeability in man; P-gp, P-glycoprotein; pKa, acid dissociation constant; $P_{trans,0,}$ membrane passive intrinsic transcellular permeability; Q_{gut}, nominal flow in gut model; REF/RAF, relative expression factor/relative activity factor; SIVA, simcyp in vitro data analysis; V_{SAC}, volume of single adjusting compartment; V_{ss}, volume of distribution at steady-state

The software's default population models for healthy subjects (Sim-Healthy Volunteers) and CYP3A substrate midazolam (Sim-Midazolam) were used in the simulations.

Model Limitations

Clinical PK data of brensocatib at single dose levels of 5 to 65 mg showed that systemic exposure to brensocatib increased in a greater than dose proportional manner between 5 mg and 35 mg with a more dose proportional increase for doses 35 mg to 65 mg (Study D6190C00001, part 1a). The Applicant hypothesized the dose-dependent exposure was due to saturation of intestinal P-gp efflux. The PBPK model of brensocatib could not reproduce this observation. The model could fairly describe the steady state pharmacokinetics for doses greater than 10 mg. In this review, the aim of PBPK analysis is to assess the DDI liability of brensocatib as a precipitant for CYP3A induction at the proposed therapeutic dose of 25 mg QD. Therefore, adequate recovery of exposure to brensocatib 25 mg QD at steady state is crucial for this application. However, brensocatib exposure at different dose levels and relative contribution of CYP enzymes and P-gp to brensocatib clearance are not considered critical for this application, thus, they are not being evaluated in this review.

Model Verification

The brensocatib PBPK model was verified using the observed PK profiles following multiple oral doses of 25 mg QD from Clinical Study D6190C00001, Part 2 in healthy subjects.

Model Application

Prediction of changes of midazolam pharmacokinetics following a single oral dose of 5 mg administered in the absence of brensocatib and on the 11th day of 14 days of brensocatib dosing with 25 mg QD, in healthy subjects.

Results

Predictive Performance of PBPK Model to Describe Brensocatib Pharmacokinetics at 25 mg QD Steady State

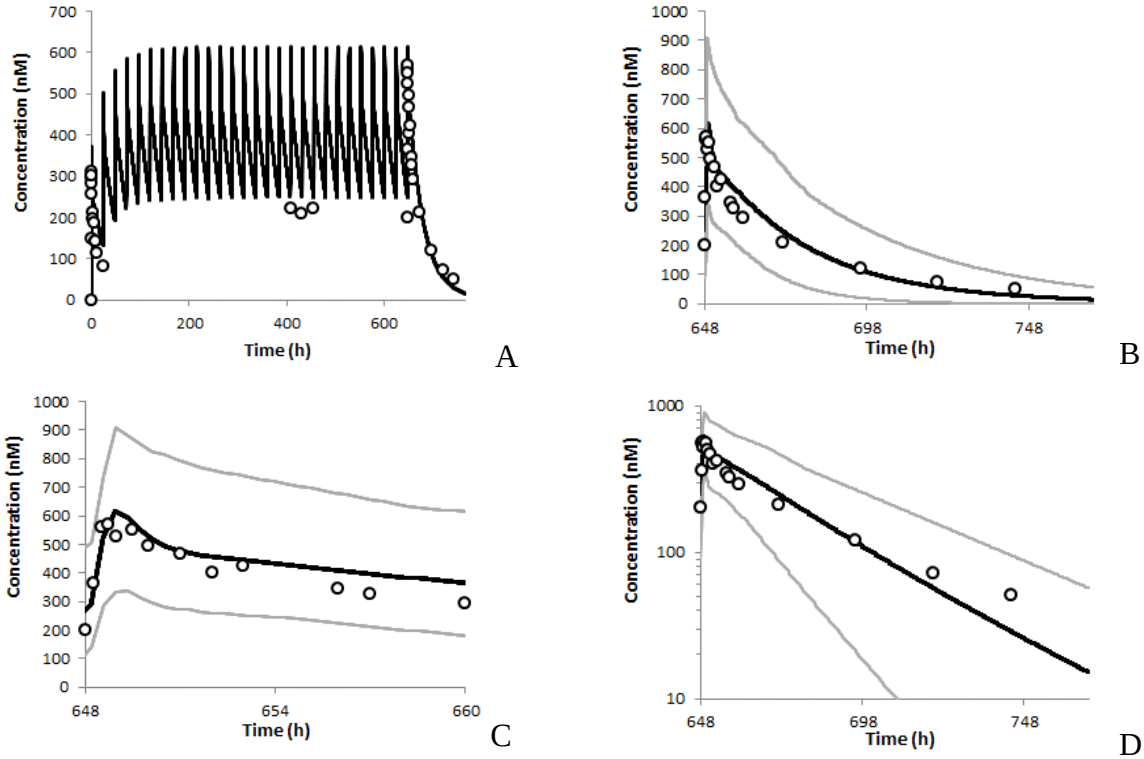
The PBPK model of brensocatib reasonably predict the observed pharmacokinetics of 25 mg QD dosing at steady state in healthy subjects (Study D6190C00001). The comparison of observed and predicted PK parameters and profile for Day 28 of 25 mg QD dosing of brensocatib is listed in Table 100 and Figure 65. The predicted median T_{max} was 1.05 h (min-max =0.65-2.35 hours) compared to observed median T_{max} of hour 0.75 h (min-max =0.52-2.0 hours).

Table 100. Predicted and Observed PK Parameters of Brensocatib 25 mg QD (Day 28) in Healthy Subjects

PK Parameters	AUC (h.nM)	C_{max} (nM)	Half-Life (h)
Predicted	14355	602	27.5
Observed	14320	598	33.8
Pred/Obs	1.00	1.01	0.81

Source: simulation output file v07b-25-mg-qd
AUC and C_{max} parameters are geometric mean values, half-life parameter is mean value.
Observed data: Study D6190C00001
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; Pred/Obs, ratio of predicted/observed value; QD, once daily

Figure 65. Predicted and Observed Plasma Concentration-Time Profiles of Brensocatib 25 mg QD



Source: simulation output file v07b-25-mg-qd
PK profile of brensocatib following multiple dosing of 25 mg QD to healthy subjects. (A) Linear PK from Day 1 and Day 28. (B) Linear PK from Day 28. (C) Linear PK for Day 12, 12 hours post-dose. (D) Log-linear PK from Day 28. Observed data from Study D6190C00001) (circles, mean of n=6 subjects). Black line: mean for the predicted population (N=60, n=6 x 10 trials). Grey lines: 5th -95th percentiles.
Abbreviation: QD, once daily

Prediction of Interaction Effect of Brensocatib 25 mg QD on the Pharmacokinetics of a Sensitive CYP3A Substrate

In vitro data showed that brensocatib increases CYP3A4 mRNA levels in a concentration dependent manner in hepatocytes in 1 out of 3 donors ('Donor 1': 1.5- to 2.5-fold for 2.2 ng/mL to 700 ng/mL and 4.48-fold at 2200 ng/mL [3.42% of the positive control rifampin], Report 8492164). The induction parameters of brensocatib (Ind_{C50} and Ind_{max}) were estimated based on the response of mRNA expression in this 'Donor 1' hepatocyte to brensocatib and calibrated to generated induction response of rifampicin (CYP3A4 inducer) in the same donor. An Ind_{C50} value of 3.24µM and Ind_{max} of 1.75-fold, were used as model input parameters.

DDI simulations were conducted to evaluate the induction effect potential of brensocatib 25 mg QD on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam (single 5 mg oral dose on Day 14). Predicted geometric mean ratios of AUC_{inf} and C_{max} for midazolam in the absence and presence of multiple dosing of brensocatib 25 mg QD at steady state are listed in Table 101. No induction effect (AUC ratio >0.8) on the pharmacokinetics of midazolam was predicted.

Sensitivity analysis was conducted by this reviewer to evaluate the impact of uncertainty in estimated induction potency on the DDI risk prediction. Increasing CYP3A4 induction potential, by reducing the Ind_{C50} value by 10-fold, had minor impact on the predicted DDI potential (no

clinical DDI risk, Table 101). Further reduction of the in vitro generated Ind_{C50} value by around 20-fold (95% reduction of value) would be needed to result in a shift towards a weak DDI effect on midazolam (AUC ratio >0.5 and ≤0.8). A weak DDI effect is still predicted with a 100-fold lower Ind_{C50} value.

Table 101. Predicted Interaction Effect of Brensocatib 25 mg QD on the Pharmacokinetics of Midazolam

Sensitivity Analysis of CYP3A4 IndC50 Parameter Value	Brensocatib CYP3A4 Induction Parameters		Midazolam Pharmacokinetics	
	Ind_{max} (Fold)	Ind_{C50} (μM)	AUC_{inf} GMR [5th-95th Percentile]	C_{max} GMR [5th-95th Percentile]
In vitro	1.75	3.24	0.92 [0.80-1.00]	0.94 [0.84-1.00]
10-fold lower	1.75	0.324	0.85	0.87
20-fold lower (95% reduction)	1.75	0.15	0.78 [0.56-0.98]	0.82 [0.63-0.99]
100-fold lower	1.75	0.0324	0.65	0.72

Source: Reviewer's analysis
Predicted geometric mean ratios (GMRs) of C_{max} and AUC_{inf} for midazolam (5 mg SD) calculated as C_{max} and AUC_{inf} in the presence/absence of brensocatib 25 mg QD.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; Ind_{C50}: concentration that gives half maximal fold induction; Ind_{max}: maximum fold induction; PK, pharmacokinetic; QD, once daily

This reviewer notes that currently there is low confidence in predicting CYP induction using the PBPK approach since there are limited data showing that CYP induction can be accurately predicted using induction parameters generated from the in vitro hepatocyte induction studies.

The Applicant provided documentation aiming to support that the PBPK software platform has been adequately qualified to predict CYP3A induction from in vitro data. The verification analysis used around 20 clinical DDI studies of drug substrates with different fraction metabolized by CYP3A4 and CYP3A inducers with varying induction potencies. The reviewer noted that based on verification documents of the software's PBPK models for CYP3A inducers, CYP3A induction parameters were optimized with clinical DDI data to adequately predict the observed induction effects. Therefore, this documentation could not be used to fully support the establishment of in vitro-in vivo extrapolation of CYP3A induction parameters.

Nonetheless, the sensitivity analysis of in vitro generated Ind_{C50} value, conducted by the reviewer, aimed to evaluate the impact of the in vitro-in vivo extrapolation uncertainty in the predicted DDI potential of brensocatib as a clinical CYP3A4 inducer. This assessment indicated a low risk for a clinical DDI liability of brensocatib 25 mg QD on CYP3A4 substrates.

14.6. Pharmacogenetics

Not applicable to this review.

15. Study/Trial Design

15.1. Study 301

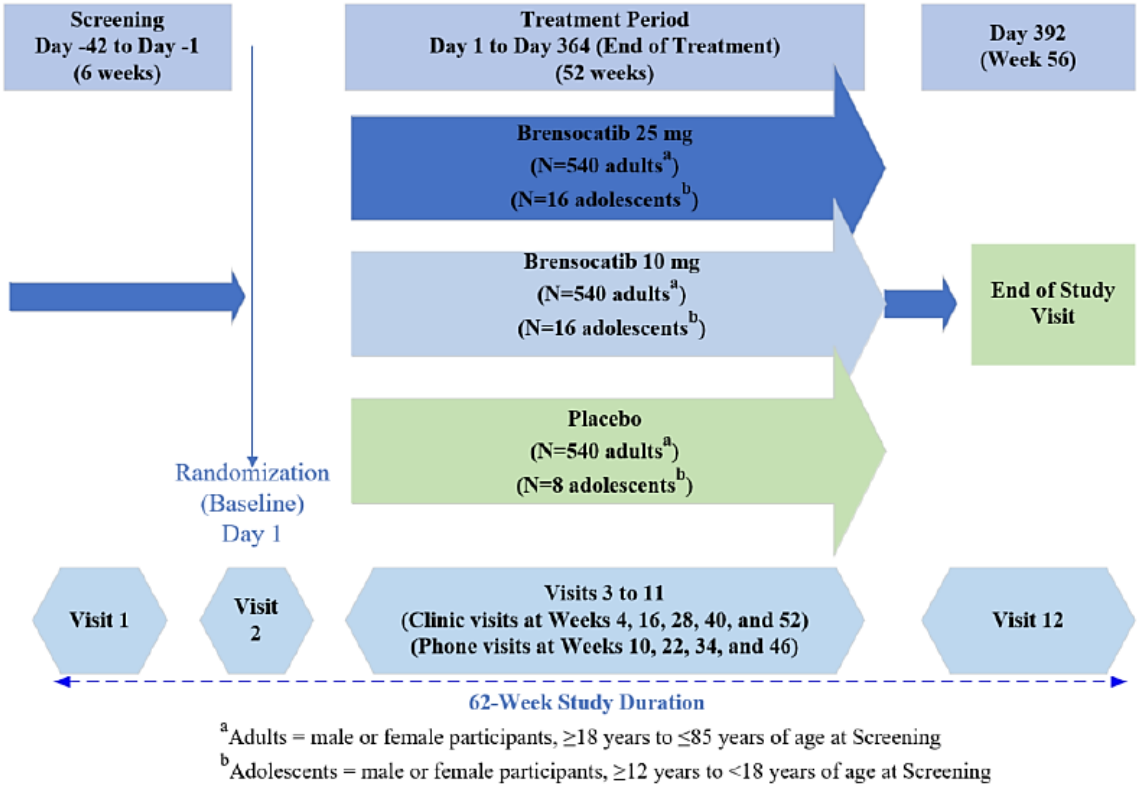
15.1.1. Overview, Study 301

Study 301 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy, safety, and tolerability of oral brensocatib 10 mg and 25 mg compared to placebo in adult and adolescent subjects ages 12 years and older with NCFB. The trial took place from November 11, 2020 (first subject visit) to March 28, 2024 (last adult subject completed the 52-week treatment period).

15.1.1.1. Study Design, Study 301

Following a 6-week screening period, adult subjects were randomized 1:1:1 and adolescent subjects were randomized 2:2:1 to brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD, respectively, for a total of 52 weeks as shown in Figure 66.

Figure 66. Study 301Schematic, Study 301



[a]Adults = male or female participants, ≥18 years to ≤85 years of age at Screening
[b]Adolescents = male or female participants, ≥12 years to <18 years of age at Screening

Source: Applicant provided (INS1007-301-protocol-original.pdf, Version 7.0, Figure 1)

There were no stratification criteria for adolescent subjects. Randomization of adults was stratified based on:

- Geographic region defined as North America, Europe, Japan, and the Rest of the World. Enrollment targets were established with up to 13% of adults from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 25% each
- Sputum sample testing for the presence of *P. aeruginosa* at Baseline
- Number of PExs, 2 or >3, in the previous 12 months.

Study 301 included two substudies:

- Pharmacokinetic/pharmacodynamic Substudy-Designed to include ~300 adults not receiving cyclic antibiotics at baseline and from whom additional blood PK and sputum PD samples were collected. Blood PD samples were collected from ~40 of these adult subjects. Blood PK and sputum PD samples are collected from all adolescents not receiving cyclic antibiotics at baseline (blood PD samples were not collected from adolescents).
- Computed tomography scan sub-study-designed to include approximately 225 adults to undergo high-resolution CT scanning at Screening and End of Treatment.

Incorporated into the design of Study 301 were 3 monitoring committees outlined below:

- An independent data monitoring committee (iDMC) monitored the safety of trial subjects, ensured the study was conducted at the highest scientific and ethical standards, and made recommendations based on the available data. No safety signals were identified by the iDMC and therefore no modifications to the study were recommended.
- An independent clinical endpoint committee adjudicated all PEx that occurred after randomization in a blinded manner to determine if the events fulfilled the protocol definition of a PEx, did not meet the definition but were considered clinically relevant, or were not considered exacerbations.
- An independent steering committee provided study oversight that included but was not limited to medical, scientific, operational, safety and external communication of the trial.

15.1.1.2. Objectives and Endpoints, Study 301

The primary objective of Study 301 was to evaluate the efficacy of brensocatib at 10 mg and 25 mg compared to placebo in subjects with NCFB. The primary endpoint for Study 301 was the annualized rate of adjudicated PExs. Pulmonary exacerbations were defined by the Hill criteria (Hill et al. 2017) as having ≥3 of the following symptoms for at least 48 hours, resulting in a physician's decision to prescribe systemic antibiotics:

- Increased cough
- Increased sputum volume or change in sputum consistency
- Increased sputum purulence
- Increased breathlessness and / or decreased exercise tolerance

- Fatigue and/or malaise
- Hemoptysis

A minimum of 14 days must have occurred between the end date of one PEx and the start date of the next PEx. Any exacerbations that occurred fewer than 14 days from the PEx were not considered a new exacerbation. All PEx were adjudicated by an independent adjudication committee composed of pulmonary physicians who review all reported PEx to determine if they fulfilled the protocol definition.

Key secondary endpoints in order of statistical hierarchy included:

- Time to first PEx
- Responder status for exacerbation-free
- Change in postbronchodilator FEV1 at Week 52
- Annualized rate of severe PEx
- Change in QoL-B Respiratory Symptoms domain score at Week 52

Secondary objectives and their corresponding endpoints outlined by the Applicant include:

- Evaluate the safety of brensocatib compared with placebo based on the incidence of adverse events and abnormalities in clinical laboratory parameters, vital signs, and ECGs
- Evaluate brensocatib exposure in adults and adolescents through the measurement of brensocatib plasma concentrations over time.

The Applicant outlined several exploratory endpoints for Study 301 as summarized below:

- Average daily change from baseline in bronchiectasis exacerbation symptom tool (BEST) score over the 52-week treatment period
- Duration of adjudicated PExs over the 52-week treatment period
- Days hospitalized due to adjudicated PEx per patient year over the 52-week treatment period
- Days of absence from work/school due to adjudicated PEx per patient year over the 52-week treatment period
- Change from Baseline in prebronchodilator and postbronchodilator FEV1, forced vital capacity (FVC), peak expiratory flow rate, percent predicted forced expiratory volume (ppFEV1), and forced expiratory flow (FEF)(25-75%) at Weeks 16, 28, 40, 52 and over 52 weeks
- Outpatient visits, emergency room visits, and hospitalizations for any reason
- Change in Quality of Life–Primary Ciliary Dyskinesia (QOL-PCD) domain scores from Baseline to weeks 16, 28, 40, 52 and over 52 weeks in adolescent subjects (>12 to <18 years of age) with PCD
- Change from Baseline in EQ-5D-5L score from Baseline to Week 52
- Change from Baseline in QOL_B domain scores at weeks 16, 28, 40, and 52 in adults
- Change from Baseline in PGIS and PGIC at weeks 16, 28, 40, and 52 in adults

- Rate of Change in prebronchodilator and postbronchodilator FEV1 over the 52-week treatment period
- Change from Baseline in BEST-CT and Airway-Artery scores at Week 52
- Change in concentration of sputum NE, CatG, and PR3 from Baseline to Week 52
- Change in concentration in blood NE, CatG, PR3, and neutrophil functions from Baseline to Week 52
- Estimated PK parameters using population PK analysis approach
- Relationships between brensocatib exposure and response (safety, efficacy, and biomarker measurements) over the 52-week treatment period.

15.1.2. Study Population, Study 301

Inclusion Criteria

- Able to provide signed informed consent. In the case of adolescents, must have signed study assent form and the adolescent's parent or legal guardian must have provided signed informed consent for the adolescent to participate.
- Adult males or females aged >18 years and <85 years at screening. Adolescent males or females aged >12 to <18 years at Screening.
- Body mass index (BMI) >18.5 kg/m2 for adults and weight >30 kg for adolescents at Screening
- Clinical history consistent with NCFB (cough, chronic sputum production and / or recurrent respiratory infections) that is confirmed by chest CT demonstrating bronchiectasis affecting one or more lobes (confirmation may be based on prior chest CT)
  - The most recent chest CT scan (but not older than 5 years before Screening date) was selected for transfer to the central reading facility for confirmation of NCFB diagnosis.
  - If the CT scan cannot be read by the reviewers due to quality issues or if a chest CT scan within the last 5 years was not available, then a new high resolution CT scan was performed and read by the central reading facility.
- Postbronchodilator FEV1 at the Screening Visit >30% of predicted normal value, calculated using the National Health and Nutrition Examination Survey reference equations and must have an absolute value >750 mL.
- Adults Only: Current sputum producer with a history of chronic expectoration of at least 3 months in the past 12 months, and able to provide a sputum sample without the need for an induction during Screening (Visit 1). If the subject was unable to produce sputum spontaneously at Screening, then they were a failure.
- Mucopurulent or purulent sputum color assessed at the Screening Visit by color chart developed by MP Murray (Murray et al. 2009). Adolescents who are unable to produce sputum were exempt from this requirement.

- At least 2 PExs defined by the need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before the Screening Visit.

Exclusion Criteria

Bronchiectasis History

- Primary diagnosis of COPD or asthma as judged by the Investigator. Patients with comorbid COPD and / or asthma were eligible for enrollment if bronchiectasis was their primary diagnosis.
- Subjects who were receiving supplemental oxygen >12 hours per day.
- Bronchiectasis due to cystic fibrosis.
- No evidence of bronchiectasis according to bronchiectasis-computed tomography (BE-CT) scoring system.
- Suffering an exacerbation 4 weeks before Screening or during the Screening period.

Infection History

- Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the investigator.
- Known history of HIV infection
- Established diagnosis of hepatitis B viral infection at the time of Screening or positive for HBsAg at the time of Screening.
- Established diagnosis of HCV infection at the time of Screening. Subjects positive for hepatitis C antibody are eligible for the study only if HCV RNA is negative.
- Currently being treated for non-tuberculosis mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis.
- Active and current symptomatic infection by COVID-19.

Background Therapy

- Started oral or inhaled antibiotics as chronic treatment for NCFB <3 months prior to the Screening Visit.
- Subjects on antibiotics as chronic treatment were on such treatment for at least 3 months prior to Screening while meeting all other inclusion criteria and none of the exclusion criteria.
- Chronic treatment with oral steroids (irrespective of the indication) was prohibited.
- Subjects who have adjustments to their baseline medications within 1 month before Screening. These subjects were eligible to be rescreened a month after the new treatment had been initiated.

Other Medical History

- Active liver disease or hepatic dysfunction manifested as follows:
  - ALT or AST >3x ULN
  - Total bilirubin >2x ULN (isolated bilirubin >2x ULN was acceptable if bilirubin is fractionated, and direct bilirubin is <35%)
  - Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones
  - Child-Pugh class C
- Abnormal renal function at Screening (eGFR <30mL/min by Chronic Kidney Disease-Epidemiology Collaboration equation formula)
- An absolute neutrophil count <1,000/mm3 at the Screening visit.
- History of malignancy in the past 5 years, except completely treated in situ carcinoma of the cervix and completely treated nonmetastatic squamous or basal cell carcinoma of the skin.
- Diagnosed with periodontal disease and were either currently treated by a dentist for this condition at Screening or expected to have periodontal disease-related procedures within the study period.
- Clinical diagnosis of Papillon-Lefèvre syndrome
- Current smokers as defined by the CDC as an adults who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.

Other Pertinent Exclusions

- Unable to perform technically acceptable spirometry that meet the ATS/ERS acceptability criteria with at least 3 acceptable flow-volume curves, at least 2 of which meet the ATS/ERS repeatability criteria for FEV1 during Screening.

Concomitant Medications

The Applicant prespecified the following medications as prohibited during the trial.

- Use of any immunomodulatory agent within 4 weeks before Screening that included but was not limited to: bortezomib, ixazomib, thalidomide, cyclophosphamide, mycophenolate, Janus kinase inhibitors, IFN-gamma, and azathioprine.
- Continuous use of high dose non-steroidal anti-inflammatory drugs.
- Chronic treatment with systemic steroids for any reason. Chronic treatment was defined as >14 days of continuous use.
- Receipt of live attenuated vaccines within 4 weeks of Screening
- Use of investigational drugs within 3 months of Screening

15.1.3. Study Assessments and Procedures, Study 301

15.1.3.1. Efficacy Assessments, Study 301

Sputum

At Screening, all adult subjects were required to provide a sputum sample, and adolescents attempted to provide a sputum sample. Sputum collection must have been obtained spontaneously and without the need for induction. Screening sputum samples were used for the assessment of sputum color and whether or not *P. aeruginosa* was present for the purpose of stratification.

In the PK/PD substudy, Screening sputum sample from eligible subjects (not receiving antibiotics at Baseline), were sent to a centralized PK/PD laboratory for the measurement of neutrophil serine proteases NE, CatG, and PR3. After Screening, predose expectorated or induced sputum samples were collected at each clinic visit and sent to the PK/PD laboratory for assessment of NE, CatG, and PR3.

Spirometry

Spirometry was performed according to the ATS/ERS criteria and included pre- and postbronchodilator FEV1 and ppFEV1, FVC, $FEF_{(25-75\%)}$, and peak expiratory flow rate (Miller et al. 2005). Prebronchodilator was defined as withholding short-acting inhaled drugs within 6 hours prior to testing or withholding long-acting muscarinic bronchodilators or oral therapy with aminophylline or slow release β-agonists for 12 to 24 hours prior to testing.

Spirometry was performed in the morning at approximately the same time each visit using the same spirometer, standard techniques, and whenever possible the same technician. Three measurements fulfilling ATS acceptability and repeatability criteria were required; however, any subject unable to provide repeatable maneuvers must have an explanation provided in the electronic case report form. Subjects must have achieved at least two acceptable curves and the largest FEV1 and FVC were to be recorded for each visit after review of all acceptable curves even if they came from different curves.

Chest CT

Screening chest CTs were collected, de-identified, and coded by study site for centralized scoring by the independent core laboratory LungAnalysis, Erasmus MC, The Netherlands. CTs were assessed by a certified observer to confirm diagnosis of bronchiectasis using the BE-CT scoring system. If no or only minor bronchiectasis was identified, the CT was further evaluated by a board-certified LungAnalysis chest radiologist to make a final determination.

The BE-CT scoring system assesses the presence or absence and the extent of bronchiectasis by each lobe creating a total sum score across a total of six areas (the lingula was assessed as a 6^{th} lobe) using the following point-based method:

- 0 = no bronchiectasis
- 1 = bronchiectasis is present in 0-32% of the lung lobe

- 2 = bronchiectasis present in 33-66% of the lung lobe
- 3 = bronchiectasis present in 67-100% of the lung lobe

CT Scan Substudy

For the CT scan substudy, adult subjects underwent guided inspiratory and expiratory high resolution CT scans at Screening and at the end of the 12-months of treatment. The substudy aimed to enroll 225 subjects with 75 subjects per study arm. As with Screening CTs, substudy CTs were centrally read by LungAnalysis. Participating sites received a CT substudy manual and were certified through the LungAnalysis Core Laboratory including training of respiratory therapy personnel, site radiologist, and site pulmonologist and characterization of site CT scanner.

Subject Reported Outcomes

In Study 301, six PRO measures were administered to subjects. The Quality of Life-Bronchiectasis PRO is discussed in detail in Section 6.3.3 of this review. The remaining five PROs are summarized below:

- Bronchiectasis exacerbation and symptoms tool (BEST) is a daily symptom diary for the assessment of bronchiectasis symptom burden and detection of exacerbations. Adult subjects were required to complete the diary daily from Screening through the end of trial visit at Week 56. Subjects were required to maintain a >75% compliance with diary entries between trial visits.
- Patient Global Impression of Change and PGIS are both 1-item questionnaires using a Likert 7-point and 5-point categorical scales, respectively, and they used to assess subjects' overall perception of change and severity in NCFB status.
- EQ-5D-5L is a two-page instrument composed of a descriptive system and visual analogue scale and developed for use in subjects ages 12 years and older. The descriptive system assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and the visual analogue scale allows respondents to report their perceived health status with a grade ranging from 0 (worst possible) to 100 (best possible). All adult and adolescent subjects completed the EQ-5D-5L on site at specified trial visits.
- The QOL-PCD questionnaire comes in four age-specific versions and consists of nine subscales to assess physical function, vitality, emotional function, treatment burden, upper respiratory symptoms, lower respiratory symptoms, social function, and hearing. All adolescents in whom PCD was the cause of their NCFB completed the QOL-PCD at specified time points.

Bronchiectasis Severity Index

The BSI scoring system is based on a combination of clinical, radiographic, and microbiological features used to assess NCFB severity. For Study 301, the BSI score was calculated at Baseline using the criteria outlined in Table 102 where a point value is assigned to each of the criteria in the first column. The total summation of these points equates to the subject's BSI score.

Table 102. Calculation of Bronchiectasis Severity Index

Severity Criteria	0 Point	1 Point	2 Point	3 Point	4 Point	5 Point	6 Point
Age (Years)	<50	-	50-69	-	70-79	-	80+
BMI (kg/m^2)	>18.5	-	<18.5	-	-	-	-
FEV1 (% predicted)	>80%	50-80%	30-49%	<30%	-	-	-
Hospital admissions due to bronchiectasis exacerbation in the past 2 years	No	-	-	-	-	Yes	-
Exacerbation frequency in last 12 months	0-2	-	3 or more	-	-	-	-
MRC dyspnea score	1-3	-	4	5	-	-	-
Colonization status	Not colonized	Chronic colonization with any pathogenic organism	-	*P. aeruginosa* colonization	-	-	-
Radiological severity	<3 lobes involved	3 or more lobes or cystic changes	-	-	-	-	-

Source: Clinical reviewer extracted from ins1007-301-protocol-original.pdf, Version 7.0, Appendix 2.
Underlined text added by Clinical reviewer based on published BSI guidelines (Chalmers et al. 2014).
Abbreviations: BMI, body mass index; BSI, Bronchiectasis Severity Index; FEV1, forced expiratory volume in 1 second; MRC, Medical Research Council; Pa, *Pseudomonas aeruginosa*

15.1.3.2. Safety Assessments, Study 301

Safety Assessments

Safety evaluations included measurement of vital signs and pulse oximetry at all study visits, physical examination including height and weight measurements at screening and Week 52, electrocardiogram at Screening and 5 specified study visits, and clinical laboratory assessments at all study visits.

Adverse Events and Serious Adverse Event Definitions

An adverse event was defined appropriately as any untoward medical occurrence or clinical investigation in a subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment. Because pulmonary exacerbations were collected as efficacy assessments, they were not reported as AEs unless they fulfilled seriousness criteria.

An SAE was appropriately defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization/prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event.

Adverse Events of Special Interest

Adverse events of special interest were defined as events known to be related to the clinical phenotype of PLS caused by the genetic deficiency of DPP1: hyperkeratosis, infections, and gingival/periodontal disease. Specific monitoring procedures and study discontinuation criteria were defined for hyperkeratosis and gingivitis/periodontitis.

Hyperkeratosis

Skin examinations, especially of the palmar/plantar surface, hand/feet dorsal surfaces, Achilles tendon area, knees, and elbows, were performed by the Investigator at Baseline and every 12 weeks beginning at Week 4. Any signs or symptoms of hyperkeratosis or erythema or deterioration of the pre-existing conditions that an Investigator determined warranted further investigation resulted in a dermatologist referral for further assessment. Any skin exfoliation or signs of skin thickening always resulted in dermatologist referral. If a subject was referred to dermatology, all subsequent skin evaluations were performed by the dermatologist at an interval determined by the dermatologist's discretion. Decisions to discontinue the subject from the trial were made by the Investigator after consulting with the dermatologist.

Gingivitis/Periodontitis

Adults were advised to conduct self-monitoring of oral soft tissue, gingiva, and tooth mobility to report to the Investigator at trial visits. Question about the presence or absence of any periodontal complaint was asked at every study visit including telephone visits. Oral and dental inspection for signs or symptoms of gingivitis or periodontitis were conducted by the Investigator for adolescents at each study visit. All subjects received dental hygiene education was administered at each study visit and included instructions on daily teeth brushing and flossing.

If there were signs or symptoms of gingivitis or periodontitis that warranted further evaluation upon investigator discretion, the subject was referred to a dentist/periodontist for further assessment of the presence of clinically-defined periodontitis. The occurrence of periodontitis was considered an AESI. Subjects were discontinued from the study if they developed severe periodontal disease defined by:

- Pocket depth measurement and attachment loss >6 mm on 2 or more teeth
- Have Class 3 mobility or Class 3 furcation involvement

15.1.4. Statistical Analysis Plan, Study 301

15.1.4.1. Sample Size Determination, Study 301

Study 301 was designed to demonstrate superiority of brensocatib treatment at 10 mg and/or 25 mg over matching placebo as measured by the primary efficacy endpoint of the rate of PExs for adult subjects over the 52-week treatment period. Assuming the annualized PEx rate in the placebo arm was 1.2 events with a negative binomial distribution with dispersion of 1, a total of 1,620 adult subjects randomized in a 1:1:1 ratio to brensocatib 10 mg, brensocatib 25 mg and matching placebo, respectively, would yield 90% overall power to demonstrate that at least 1 dose of brensocatib was superior to placebo under the Truncated Hochberg procedure (overall alpha =0.01; two-sided test; truncation fraction =0.9). The ratio of exacerbation rate was assumed to be 0.70 (brensocatib over placebo) between any of the brensocatib treatment arms and placebo after 52 weeks of treatment.

15.1.4.2. Sensitivity and Supplementary Analyses, Study 301

A sensitivity analysis was prespecified that investigated whether the results for the primary endpoint were robust to departure from the assumption that unobserved data were missing at random (MAR). The tipping point analysis investigated a range of progressively more conservative assumptions about the number of events occurring in the post-withdrawal period.

As the first step, multiple imputations of missing PEx data under the observed data model (MAR assumption) was implemented using negative binomial model, which models the distribution of a response Y, e.g., the number of PEx events, as the joint distribution of the observed responses Y_{mis} and a distribution of the missing responses Y_{mis} after discontinuation from the study. Missing post withdrawal PEx were imputed with the predicted PEx values from the model, per treatment and strata, for the time remaining after study discontinuation prior to Week 52.

For a given subject, the conditional distribution $Y_{mis}|Y_{obs}$ was a function of the observed events y_1, the estimated dispersion, the estimated observed PEx rate (which was the same as obtained in the primary analysis) and the model covariates. The imputed count of PEx was combined with the observed PEx count. The process of imputing missing PEx data was repeated multiple times to create 100 separate datasets.

As the second step, a penalty (delta) was applied to the imputed data prior to analyzing each of the separate data sets. For each brensocatib dose comparison relative to placebo, the tipping point penalties (delta adjustment) was applied in a bi-directional manner. That is, the PEx rate (after

imputation) for the MNAR data in the brensocatib arms was incrementally increased, while the PEx rate for the MNAR data in the placebo arm was incrementally decreased. With each increment, the 100 complete data sets were each analyzed using the same model as for the primary analysis. The analysis results for each increment were combined using Rubin's rules.

The delta penalties investigated were preselected multiples of the observed rate reduction. If the observed rate ratio reduction from the primary analysis is x, the deltas investigated ranged from 1-x to 1+3*x for both active and the placebo arms, in increments of 0.5*x.

Complete sets of exacerbation data (observed and imputed) for the three treatment arms were generated using multiple imputation under the MAR assumption. The imputation model contained the same covariates as in the primary analysis model. Missing data were assumed to be MNAR and then the corresponding delta was applied. One hundred (100) separate complete data sets for each of the relevant cells was generated and analyzed. The log-scale results were combined using Rubin's method and then exponentiated to obtain final estimates for the rates and rate ratios. The relevant delta increment/decrement grid for each brensocatib dose comparison was populated with the corresponding p-values. If a Tipping Point was identified, the plausibility of the assumptions surrounding the MNAR data (i.e., magnitude of the delta adjustments in both treatment arms) was to be assessed from a clinical perspective.

A jump-to-reference sensitivity analysis was performed in which the placebo group acted as the reference group. All data with an assessment or visit date prior to the time of the first of any intercurrent events was included. Data with an assessment or visit date after occurrence of an intercurrent event related to treatment failure (e.g., treatment discontinuation due to adverse event) was considered missing and imputed. Multiple imputations were used to replace missing outcomes.

A supplementary analysis was prespecified, which redefined the time at risk for subjects. For this analysis, the time at risk was defined as the total time on study for a subject. The duration of pulmonary exacerbations was ignored in this analysis.

Supplementary analyses were performed that repeated the primary analysis using alternative estimands. These estimands were the on-investigational product (IP) and on-treatment estimands. The treatment regimen for the on-IP estimand was the randomized IP irrespective of modifications to standard of care, but data after discontinuation was considered missing. The treatment regimen for the on-treatment estimand was the randomized IP plus standard of care without addition of new chronic antibiotics during the treatment period or modifications to chronic antibiotics taken at Baseline.

15.1.4.3. Subgroup Analyses, Study 301

The Applicant prespecified subgroup analysis based on the following:

- Age (12- <18, 18-<65 years, ≥65 years); (<75 years, ≥75 years); (>=18 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

- Number of PEx in prior 12 months (<3, ≥3)
- Chronic use of Antibiotics at Baseline (Yes, No)
- Maintenance use of macrolides at Baseline (Yes, No)
- *Pseudomonas aeruginosa* colonization at Baseline (Positive, Negative)
- (Re-calculated) BSI score (≤4, 5-8, ≥9)
- Baseline BSI score (< Median, ≥ Median)
- BE-CT score (< Median, ≥ Median)
- Baseline FEV1% Predicted (<50%, ≥50%) post-bronchodilator
- Stratification region (North America, Europe, Japan, the Rest of World)
- Geographical region (South America, Eastern Europe, Western Countries, Asian Countries, Oceania)
- Baseline eosinophil count (>=300/mm3, <300/mm3)
- Smoking status (Former smoker, Never smoked)
- Use of inhaled steroids (Yes, No)
- History of Asthma (Yes, No)
- History of Chronic Obstructive Pulmonary Disease (Yes, No)
- Hospitalized in prior 24 months for PEx (Yes, No)

15.1.4.4. Secondary Endpoints, Study 301

For the secondary endpoint of responder status for exacerbation-free over the 52-week treatment period, responder status was imputed for subjects who discontinued the study prior to Week 52 without experiencing a pulmonary exacerbation. A Bayesian piecewise exponential model was fit using eight intervals assuming piecewise constant hazards and a gamma prior. The survival estimates for each set of covariates were output and merged with the observed data. Let $\hat{S}$ be the estimated survival function, c_i be the censoring time of subject i, x_i be the covariate vector for subject i, and $\hat{\beta}$ be the estimated coefficients from the Bayesian piecewise exponential model. An event time was imputed as follows:

1. Compute $p_i = 1 - \hat{S}(c_i|x_i, \hat{\beta})$.
2. Draw a uniform random value $u_i \sim \text{uniform}[p_i, 1]$.
3. Impute event time t_i as the solution of $u_i = 1 - \hat{S}(t_i|x_i, \hat{\beta})$. This ensures that the imputed event time will be greater than the censoring time.

Step 2 was repeated 100 times creating 100 separate datasets each of which was used to estimate the event times per subject. Any subjects censored prior to Week 52 had their event time replaced with the imputed event time. Subjects with imputed event time greater than or equal to Day 365 were considered responders. Each of the 100 datasets was analyzed using a logistic regression model specified in Section 6. The results were combined using Rubin's rules.

Bayesian Analysis of Adolescent Subgroup

The negative binomial regression model for adults included treatment group, sputum sample being classified as positive or negative for *P. aeruginosa* at Screening Visit, the number of prior PExs (<3 or ≥3) in the previous 12 months, and stratification region (North America, Europe, Japan, and the Rest of the World), covariates and the logarithm of time at risk (time on study excluding the time during exacerbations) in years as an offset variable. Vague priors were selected, and a Markov chain Monte Carlo algorithm was used to draw random samples from the posterior distribution. The posterior treatment effect estimates and their covariance for adults informed the prior distribution for the adolescent data analysis.

The negative binomial regression model for adolescents was similar to the model for adults. For the treatment effect parameters, the prior distribution was a weighted mixture of a non-informative prior and a distribution of the treatment effects in adults, with the mixing weight ranging from 0 (no borrowing) to 1 (full borrowing) in increments of 0.1. A Markov chain Monte Carlo algorithm was used to draw random samples from the posterior distribution. Posterior means, variance, and 95% credible intervals were estimated for the treatment effects for both brensocatib groups compared to placebo.

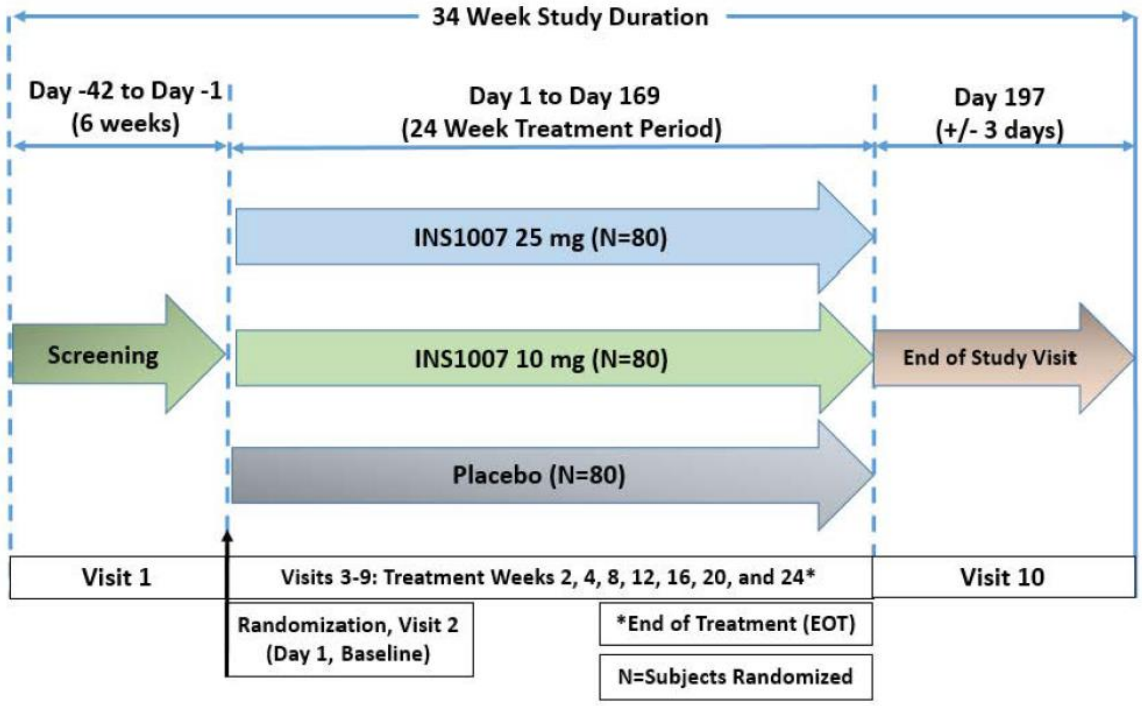
15.2. Study 201

15.2.1. Overview, Study 201

15.2.1.1. Study Design, Study 201

Study 201 was a phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of oral brensocatib 10 mg and 25 mg QD compared to placebo in subjects aged 18 years and older with NCFB. Following screening, subjects were randomized 1:1:1 to one of the three treatment arms to receive assigned treatment for 24 weeks followed by a 4-week follow-up period as shown in Figure 67.

Figure 67. Schematic, Study 201



Source: Applicant provided (ins1007-201-csr-16-1-1-protocol-amendment.pdf, Version 5.0, Figure 1).

Randomization was stratified based on whether the sputum culture at screening was positive for *P. aeruginosa* and whether the subject was on maintenance use of macrolides.

Study 201 included a PK substudy enrolling up to 36 subjects for whom underwent additional blood sampling at Visit 2 and Visit 4.

15.2.1.2. Objectives and Endpoints, Study 201

The primary objective of Study 201 was to evaluate the efficacy of brensocatib on time to first pulmonary exacerbation compared to placebo over the 24-week treatment period. The efficacy endpoints are listed below:

Primary Endpoint

- Time to first pulmonary exacerbation

Secondary Endpoints

- Change from baseline in QOL-B Respiratory Symptoms Domain at 24 weeks
- Change from Screening in postbronchodilator FEV1 at 24 weeks
- Change in concentration of active neutrophil elastase in sputum from pre-treatment to on-treatment
- Rate of pulmonary exacerbations (number of events over person-time) at 24 weeks

15.2.2. Study Population, Study 201

Inclusion Criteria Included

- Male or female between the ages of 18 and 85 years (inclusive) with a BMI >18.5 at Screening
- Diagnosed with NCFB confirmed by chest CT
- Current sputum producer with history of chronic expectoration and able to provide a sample
- Sputum color at Screening of mucoid purulent or purulent as assessed by the sputum color chart
- Documentation of at least 2 pulmonary exacerbations, defined as the need for antibiotic prescription by a physician for signs and symptoms of respiratory infections, in the last 12 months

Exclusion Criteria Included

Bronchiectasis History

- Primary diagnosis of COPD or asthma
- Bronchiectasis due to cystic fibrosis, hypogammaglobulinemia, CVID, or AATD
- Current treatment for a nontuberculosis mycobacterial lung infection, allergic bronchopulmonary aspergillosis, or tuberculosis
- Acute infection requiring treatment within 4 weeks of Screening (or 12 weeks if prescribed a macrolide)
- Taking cyclic doses of antibiotics as chronic treatment for NCFB or chronic oral or inhaled antibiotics <6 months prior to Baseline
- Not on a stable dose of an inhaled corticosteroid for at least 4 weeks prior to Day 1

Other Medical and Laboratory History

- Abnormal renal function test defined as an eGFR <45 mL/min by chronic kidney disease epidemiology collaboration equation at screening
- Elevated liver function test results defined as an ALT or AST >2x ULN at Screening
- A bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at Screening
- A white blood cell count < lower limit of normal at Screening
- Have a baseline-corrected QTcF >450 milliseconds (males) or 470 milliseconds (females) or history of congenital long QT syndrome, or Torsades de Pointes or other abnormal ECG at Screening or Baseline (unless the ECG findings are not clinically significant and are approved by the Investigator and documented by signature)

- Concomitant medications with the potential to cause hyperkeratosis or are CYP3A4/5 inducers or CYP3A4/5 inhibitors when combined with CYP2D6 and CYP3C8 inhibitors
- Current smoker
- Have a clinical diagnosis of PLS

Have the Following Medical Conditions Associated With the Onset of Non-hereditary Palmoplantar Keratosis

- Hypothyroidism, myxedema, chronic lymphedema, acrocyanosis, or livedo reticularis
- Have psoriasis or lichen planus
- Have Reiter's disease/keratoderma, or blennorrhagicum, or "reactive arthritis"
- Have pityriasis rubra pilaris, or atopic dermatitis, or chronic hand dermatitis, or chronic contact dermatitis, or chronic dermatophytosis
- Have chloracne, or extensive verruca vulgaris, or keratoderma climactericum
- Perform extreme running or swimming, or other chronic, repetitive mechanical or water damage to plantar epidermis

Periodontal Disease (To Be Evaluated by a Periodontist or Dentist)

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

15.2.3. Study Assessments and Procedures, Study 201

15.2.3.1. Efficacy Assessments, Study 201

Efficacy evaluations included sputum collection for PD assessment (neutrophil elastase concentration), spirometry, BSI score, and administration of the QOL-B. These procedures were conducted under the same conditions as outlined for Study 301 (Section 15.1.3.1). As with Study 301, an NCFB pulmonary exacerbation was defined using the Hill criteria for Study 201 (Section 15.1.1.2).

15.2.3.2. Safety Assessments, Study 201

Safety Assessments

Safety evaluations included measurement of vital signs, physical examinations, electrocardiograms, hematology and blood chemistry values, skin evaluations, dental examinations, and adverse events.

Adverse Events and Serious Adverse Events

Adverse events and SAEs were appropriately defined and consistent with the definitions in Study 301 (Section 15.1.3.2).

Adverse Events of Special Interest

As in Study 301, AESIs were defined as evens known to be related to treatment with DPP1 inhibition: hyperkeratosis, gingival / periodontal disease, and infections.

Hyperkeratosis

A skin examination, particularly of the palms, soles, dorsum of hands and feet, Achilles tendon area, knees, and elbows, was performed by the Investigator at each study visit. Signs or symptoms of hyperkeratosis, erythema, or deterioration of preexisting conditions resulted in a referral to dermatology for further evaluation and follow-up in the same manner described for Study 301 (Section 15.1.3.2). Discontinuation decisions were made by the Investigator after consulting with the dermatologist.

Gingivitis/Periodontitis

All subjects underwent dental examinations by a dentist at Baseline, Week 8, and Week 24. Baseline (Screening) examinations included a full-mouth dental radiography and evaluation of oral soft tissue, gingiva and teeth by a study designated local dentist, and eligible subjects received a dental deep cleaning (scaling and root planing) before randomization. Subjects underwent dental inspection by the Investigator for signs and symptoms of oral infection, gingivitis, or periodontitis or deterioration of preexisting conditions at each study visit which if identified prompted referral to the study-designated dentist for further evaluation and standard of care treatment.

Subjects were advised to conduct self-monitoring of oral soft tissue, gingiva, and tooth mobility to report their findings to the Investigator at each visit. Subjects received dental hygiene counseling at each study visit including guidance on daily teeth brushing and flossing.

Any occurrence of gingivitis, periodontitis, or tooth loosening during the study were considered an AE. Subjects with severe gingivitis/periodontitis were discontinued from the study at the discretion of the Investigator.

Withdrawal and Early Discontinuation Criteria

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

- Subject death
- Subject experiences an AE(s)/SAEs that warrants discontinuation, as judged by the Investigator and/or Insmed
- A major protocol deviation, which, in the opinion/discretion of the Investigator and/or Insmed compromises the data integrity of the study
- Subject is noncompliant with the study drug treatment
- Treatment code is prematurely broken by the Investigator
- Subject withdraws consent
- Subject decision to discontinue treatment
- Applicant terminates the study
- Investigator discretion
- Subject lost to follow-up
- Subject pregnancy
- Periodontal criteria met
- Skin criteria met
- Serious infection, defined as life-threatening infections, infections requiring hospitalization, or infections requiring treatment with intravenous antibiotics (except hospitalizations for exacerbations, where the principal investigator will evaluate whether it is in the best interest of the subject to continue in the study)
- Subjects who develop neutropenia defined as ANC <1000/mm3

15.2.4. Statistical Analysis Plan, Study 201

15.2.4.1. Sample Size Determination, Study 201

The sample size determination for Study 201 assumed that that pulmonary exacerbations would occur at a rate of 1.2 events per subject year in the placebo group, corresponding to 44.6% of the placebo subjects being event free at 24 weeks. It was expected that 40% more event free subjects would be observed within both brensocatib groups, corresponding to 62.4% of the brensocatib subjects being event free at 24 weeks. Thus, the hazard ratio used in the sample size calculation was ln(0.624)/ln(0.446) =0.584. The randomization ratio was 1:1:1 to 3 treatment arms. If the expected difference in time to the first event was 40% after 24 weeks of treatment with Type I error of one-sided alpha =0.1, then 216 subjects in total with 72 completers per arm, would yield 80% power. Approximately 240 subjects diagnosed with NCFB were planned to be randomized

to provide approximately 216 subjects to complete the study, assuming 10% of the subjects would discontinue study drug before completing 24 weeks of treatment.

15.2.4.2. Sensitivity and Supplementary Analyses, Study 201

The primary analysis was performed for the PP analysis set as a supplementary analysis. The PP analysis set was defined as all subjects who were randomized and completed the study without any major deviations.

As a sensitivity analysis, the time to first pulmonary exacerbation was analyzed using a stratified Cox proportional hazards model with treatment group as a covariate, stratified by *P. aeruginosa* colonization status and maintenance antibiotic use at Baseline.

15.2.4.3. Subgroup Analyses, Study 201

Subgroup analyses of the time to first pulmonary exacerbation used the stratified (by *P. aeruginosa* colonization status and maintenance antibiotic use at baseline) and unstratified Cox proportional hazards models. Prespecified subgroups were as follows:

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

Additionally, post hoc analyses were requested from the Applicant for subgroups of gender (Female, Male), race (White, Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino).

15.2.4.4. Testing Hierarchy, Study 201

Overall Type I error control was specified as one-sided alpha of 0.1 and testing hierarchy was as follows. The primary endpoint was first tested at one-sided alpha of 0.1 for the 25-mg dose. If significant, then the alpha was split equally between the primary endpoint for the 10-mg dose and the key secondary endpoints for the 25-mg dose. If the primary endpoint for the 10-mg dose was significant, then the key secondary endpoints for the 10-mg dose were tested. Among the key secondary endpoints for each dose, testing was performed using the Holm-Bonferroni method.

15.2.4.5. Secondary Endpoints, Study 201

The review team focused on the primary endpoint for Study 201. The descriptive analysis methods and results for secondary endpoints provided supportive information.

Change from screening in post-bronchodilator percent predicted FEV1 at Week 24 was analyzed using analysis of covariance with *P. aeruginosa* colonization status and maintenance antibiotic use at baseline as covariates. Only subjects with data at Week 24 were included in the analysis, and so assumes data were missing completely at random. The least squares means and mean treatment differences were estimated as well as 95% confidence intervals. The statistical reviewer conducted a post hoc sensitivity analysis which assumes data MAR using a linear repeated measures mixed model with the same covariates as the analysis of covariance model, as well as visit, visit by treatment interaction, and baseline value. Repeated measures from Weeks 12 and 24 were included and a compound symmetric covariance structure was used to produce a robust sandwich variance estimator. In SAS PROC MIXED, the OM option was used to adjust the coefficients for the least squares means to reflect the observed data.

The dichotomous outcome of experience of at least one pulmonary exacerbation or no pulmonary exacerbations during the 24-week treatment period was analyzed using a Cochran-Mantel-Haenszel statistic, stratified by *Pa* colonization status and maintenance macrolide antibiotic use at baseline. As an exploratory sensitivity analysis which assumes data are MAR, the rate of pulmonary exacerbations through Week 24 was analyzed using a negative binomial model with an offset of the logarithm of time at risk in years, defined as time of follow-up. Covariates of *Pa* colonization status and maintenance macrolide antibiotic use at baseline were included in a separate negative binomial model.

Change from baseline in QoL-B respiratory symptoms score over the 24-week treatment period was planned to use a mixed model for repeated measures to estimate the treatment effect averaged across the trial with equal weights for each visit.

Change in concentration of active NE in sputum from pre-treatment to on-treatment was described as a secondary endpoint but is considered an exploratory pharmacodynamic endpoint and results are not presented.

16. Efficacy

16.1. Study 301

16.1.1. Results of Sensitivity and Supplementary Analyses, Study 301

The tipping point analyses identified tipping points where p>0.01 for the comparisons between both brensocatib treatment groups with placebo. The tipping point occurred at highly conservative assumptions about the number of events occurring in the post-withdrawal period for the comparison between brensocatib 10 mg and placebo, and so the review team concluded that the results were robust to the MAR assumption for unobserved data. The tipping point occurred for somewhat less conservative assumptions for the comparison between brensocatib 25 mg and

placebo. However, the estimated treatment effect was clinically meaningful with minimal shifts across the range of penalties prespecified. The review team concluded that the results for the brensocatib 25-mg group were robust to the MAR assumption for unobserved data.

The jump-to-reference analysis used the placebo group as the reference after an intercurrent event related to study treatment and showed a statistically significant treatment effect that was similar to the primary analysis, supporting the robustness of the primary analysis.

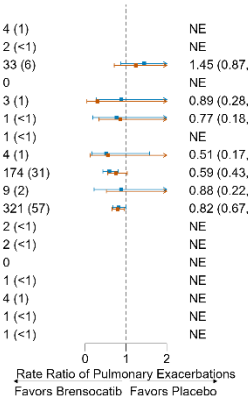
The supplementary analysis that used the time on study as the time at risk without excluding time during pulmonary exacerbations yielded substantially similar results to the primary analysis. The supplementary analysis that considered the on-IP estimand and the on-treatment estimand also yielded similar results, which supports the primary analysis.

16.1.2. Post Hoc Subgroup Analyses of Primary Endpoint, Study 301

The rate ratio of the annualized rate of pulmonary exacerbations by etiology are presented in Figure 68. Estimation was not possible for most etiologies because of sample size and the most common primary listed etiology was “Other.” Subgroup sizes were small and confidence intervals were wide where most included the null value of 1, limiting clinical interpretation.

Figure 68. Exploratory Subgroup Analysis: Forest Plot by Etiology of Rate Ratio of Pulmonary Exacerbations Through Week 52 Between Brensocatib and Placebo in ITT Analysis Set, Study 301

Variable	Brensocatib 10mg QD, n (%)	Brensocatib 25mg QD, n (%)	Placebo, n (%)	Rate Ratio (95% CI) for 10mg arm	Rate Ratio (95% CI) for 25mg arm
Etiology					
Autoimmune disease: Rheumatoid arthritis	2 (<1)	0	4 (1)	NE	NE
Autoimmune disease: Sjogren's syndrome	1 (<1)	0	2 (<1)	NE	NE
Cilia abnormalities: Primary ciliary dyskinesia	47 (8)	38 (7)	33 (6)	1.45 (0.87, 2.42)	1.24 (0.71, 2.16)
Connective tissue disease: Tracheobronchomegaly (Mounier-Kuhn syndrome)	2 (<1)	0	0	NE	NE
Hypersensitivity: Allergic bronchopulmonary aspergillosis (ABPA)	6 (1)	4 (1)	3 (1)	0.89 (0.28, 2.85)	0.3 (0.04, 2.07)
Immune deficiency: Immunoglobulin deficiency	2 (<1)	5 (1)	1 (<1)	0.77 (0.18, 3.24)	0.86 (0.34, 2.18)
Inflammatory bowel disease: Ulcerative colitis	1 (<1)	0	1 (<1)	NE	NE
Injury: Aspiration	8 (1)	5 (1)	4 (1)	0.51 (0.17, 1.58)	0.56 (0.12, 2.52)
Injury: Pneumonia/childhood infections	173 (30)	156 (27)	174 (31)	0.59 (0.43, 0.81)	0.76 (0.56, 1.03)
Injury: Smoke inhalation	6 (1)	10 (2)	9 (2)	0.88 (0.22, 3.55)	2.5 (0.52, 12.05)
Other	331 (57)	355 (62)	321 (57)	0.82 (0.67, 1)	0.8 (0.66, 0.96)
Other: Yellow nail syndrome	2 (<1)	0	2 (<1)	NE	NE
Other: α1-Antitrypsin deficiency	2 (<1)	1 (<1)	2 (<1)	NE	NE
Obstruction: Foreign body	0	1 (<1)	0	NE	NE
Connective tissue disease: Cartilage deficiency (Williams-Campbell syndrome)	0	0	1 (<1)	NE	NE
Inflammatory bowel disease: Crohn's disease	0	0	4 (1)	NE	NE
Obstruction: Tumor	0	0	1 (<1)	NE	NE
Other: Young's syndrome	0	0	1 (<1)	NE	NE



Source: Statistical reviewer analysis using adces.xpt
Abbreviations: CI, confidence interval; ITT, intent-to-treat; NE, not estimable; QD, once daily

16.1.3. Subgroup Analyses of Key Secondary Endpoints, Study 301

Subgroup analyses were prespecified by the Applicant for all key secondary endpoints and the same subgroups as used for the primary endpoint. Selected results related to change from baseline in FEV1 are presented in Section 6.3. Other subgroups and results from other key secondary endpoints were consistent with the analysis of the overall population for the respective endpoints.

16.1.4. Bronchiectasis Questionnaire for Clinical Trials, Study 301

In Study 301, the QOL-B was administered to adult patients with NCFB. Refer to Section 6.3.3 for the description of QOL-B.

16.1.4.1. Interpretation of Change From Baseline in QOL-B RSS at Week 52, Study 301

The review team considered the evidence provided in the application regarding whether the observed treatment effect substantiated a clinically meaningful improvement in respiratory symptoms for patients receiving brensocatib as compared to placebo in Study 301.

The Agency recommends the use of anchor-based methods to establish meaningful change thresholds in clinical outcome assessment-based endpoints, although other methods (e.g., qualitative evidence) can be used per the FDA draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023). The Applicant administered two anchor measures for this purpose, the PGIS and PGIC. However, the PGIS and PGIC were added to the study materials in Study 301 after study enrollment began, resulting in fewer than 20% of subjects in the ITT population with non-missing QOL-B RSS at baseline having PGIS or PGIC data that could be used to assess patient perception of meaningful change. As such the Agency's review included an assessment of the characteristics of the subsamples with and without PGIS and PGIC anchor data as well as a supplemental anchor-based analysis using an exploratory anchor, which was administered to the full sample, in order to determine whether the results of the PGIS/PGIC anchor-based meaningful change analyses were representative of the Study 301 sample.

16.1.4.2. Anchor Measures Administered, Study 301

The Applicant included the PGIS as the primary anchor and PGIC as the secondary anchor to facilitate interpretation of change in the QOL-B RSS. Specifically, the PGIS is a 1-item questionnaire to assess severity of subject's overall status on a 5-point Likert scale, ranging from "none" to "very severe." Subjects completed the PGIS via an eDiary every 2 weeks from baseline to Week 56. The PGIC is also a single-item questionnaire to assess change in subject's overall status on a 7-point Likert scale, ranging from "very much improved" to "very much worse." Subjects completed the PGIC every 2 weeks after baseline to Week 56.

The Applicant's selected anchor scales (i.e., the PGIS and PGIC) were incorporated into the study materials after enrollment began. This late addition resulted in a large number of missing scores on these anchor measures, of which only 18% of the full sample is used in the anchor-based analyses. The concept of "overall status" assessed by the PGIS and PGIC is broad and not specific to bronchiectasis symptoms and/or impacts. The 52-week recall period of the PGIC may be too long for subjects to accurately estimate change, which may introduce recall error. There is also a lack of qualitative data to support a target anchor change category(ies) on the PGIS and PGIC. All these issues collectively compromise the utility of the PGIS and PGIC as sole anchors to conduct anchor-based analyses. As such, the FDA requested the Applicant to explore additional PRO(s), specifically the UA item of the EQ-5D-5L administered alongside the QOL-B

instrument, as a complementary anchor for the evaluation and interpretation of within-patient meaningful change. However, the recall period (i.e., "today") of the UA item[2] and its concept measured are not fully aligned with the assessment period and measurement concept of the QOL-B RSS endpoint, which limits its use as an appropriate alternative anchor for conducting anchor-based analyses.

16.1.4.3. Characteristics of Subsamples With/Without PGIS/PGIC to Full Sample, Study 301

The full Study 301 sample (n=1472) with data on the QOL-B RSS endpoint is defined as the ITT population with non-missing QOL-B RSS at baseline. Of these, only 267/1472=18% had data on the PGIS and/or PGIC anchor measures (i.e., having non-missing PGIS scores at baseline and Week 52 and/or having non-missing PGIC score at Week 52). This will be referred to as the "anchor subsample" throughout this review. The Agency sent an information request dated January 29, 2025, requesting the Applicant provide demographics (see

[2] As the results of the anchor-based analyses using the full sample and the UA item were similar to those using the sub sample with PGIS/PGIC anchor-data, results of analyses using the UA item are not discussed.

Table 103, baseline characteristics (see Table 104), and distribution of QOL-B RSS among subsamples with and without PGIS/PGIC scores (see Table 105 and Table 106), to assess whether results of anchor-based analyses using the subsample with data on PGIS and PGIC, can be generalized to the full Study 301 sample.[3] Specifically, the subsamples include:

1. Anchor subsample: patients having **non-missing** PGIS score at baseline and Week 52, and/or having **non-missing** PGIC score at Week 52,
2. PGIS anchor subsample: patients having **missing** PGIS score at baseline or at Week 52 (i.e., change in PGIS from baseline at Week 52 is missing), and
3. PGIC anchor subsample: patients having **missing** PGIC score at Week 52.

[3] Full sample is defined as the ITT population with non-missing QOL-B RSS at baseline.

Table 103. Demographic Characteristics, ITT Population, Study 301

Characteristics	Non-Missing PGIS Score at Baseline and Week 52	Missing PGIS Score at Baseline or Week 52	Non-Missing PGIC Score at Week 52	Missing PGIC Score at Week 52
Stratification region, n(%)				
North America	50 (20.2)	198 (13.4)	59 (19.2)	189 (13.4)
Europe	92 (37.1)	581 (39.4)	123 (39.9)	550 (38.9)
Japan	47 (19.0)	40 (2.7)	48 (15.6)	39 (2.8)
Rest of world	59 (23.8)	654 (44.4)	78 (25.3)	635 (44.9)
Geographic region, n(%)				
South America	39 (15.7)	449 (30.5)	57 (18.5)	431 (30.5)
Eastern Europe	12 (4.8)	203 (13.8)	14 (4.5)	201 (14.2)
Western countries	120 (48.4)	502 (34.1)	152 (49.4)	470 (33.3)
Asian countries	58 (23.4)	202 (13.7)	66 (21.4)	194 (13.7)
Oceania	19 (7.7)	117 (7.9)	19 (6.2)	117 (8.3)
Age (years)				
n	248	1473	308	1413
Mean (SD)	62.0 (13.96)	59.8 (15.98)	61.3 (14.41)	59.9 (15.98)
Median	65.0	64.0	65.0	64.0
Min, max	23, 85	12, 85	23, 85	12, 85
Age group, n(%)				
12 to <18 years	0	41 (2.8)	0	41 (2.9)
18 to <65 years	118 (47.6)	723 (49.1)	149 (48.4)	692 (49.0)
>=65 years	130 (52.4)	709 (48.1)	159 (51.6)	680 (48.1)
>=18 years	248 (100)	1432 (97.2)	308 (100)	1372 (97.1)
<75 years	204 (82.3)	1257 (85.3)	255 (82.8)	1206 (85.4)
>=75 years	44 (17.7)	216 (14.7)	53 (17.2)	207 (14.6)
Sex, n(%)				
Male	84 (33.9)	530 (36.0)	104 (33.8)	510 (36.1)
Female	164 (66.1)	943 (64.0)	204 (66.2)	903 (63.9)
Ethnicity, n(%)				
Not Hispanic or Latino	194 (78.2)	967 (65.6)	231 (75.0)	930 (65.8)
Hispanic or Latino	45 (18.1)	466 (31.6)	65 (21.1)	446 (31.6)
Not reported	9 (3.6)	34 (2.3)	11 (3.6)	32 (2.3)
Unknown	0	6 (0.4)	1 (0.3)	5 (0.4)

Characteristics	Non-Missing PGIS Score at Baseline and Week 52	Missing PGIS Score at Baseline or Week 52	Non-Missing PGIC Score at Week 52	Missing PGIC Score at Week 52
Race, n(%)				
American Indian or Alaska Native	0	23 (1.6)	0	23 (1.6)
Asian	48 (19.4)	143 (9.7)	50 (16.2)	141 (10.0)
Black or African American	2 (0.8)	8 (0.5)	2 (0.6)	8 (0.6)
Native Hawaiian or other Pacific Islander	0	2 (0.1)	0	2 (0.1)
White	169 (68.1)	1097 (74.5)	218 (70.8)	1048 (74.2)
Other	1 (0.4)	38 (2.6)	2 (0.6)	37 (2.6)
Asian/Maori	0	1 (0.1)	0	1 (0.1)
Australian Aboriginal	0	1 (0.1)	0	1 (0.1)
Brown race	0	1 (0.1)	0	1 (0.1)
Latin	0	1 (0.1)	0	1 (0.1)
Latino	0	1 (0.1)	1 (0.3)	0
Maori	0	1 (0.1)	0	1 (0.1)
Mestizo	0	5 (0.3)	0	5 (0.4)
Mexican	0	3 (0.2)	0	3 (0.2)
Mixed	0	3 (0.2)	0	3 (0.2)
Mixed race	0	14 (1.0)	0	14 (1.0)
Mulatto	0	5 (0.3)	0	5 (0.4)
New Zealand Maori	0	1 (0.1)	0	1 (0.1)
Other mixed	0	1 (0.1)	0	1 (0.1)
Puerto Rican	1 (0.4)	0	1 (0.3)	0
Unknown	6 (2.4)	39 (2.6)	8 (2.6)	37 (2.6)
Not reported	22 (8.9)	86 (5.8)	28 (9.1)	80 (5.7)
Multiple	0	37 (2.5)	0	37 (2.6)
Height (cm) at Screening				
n	248	1473	308	1413
Mean (SD)	164.62 (9.633)	164.05 (9.784)	164.70 (9.744)	164.01 (9.764)
Median	165.00	163.00	165.00	163.00
Min, max	141.4, 195.6	140.0, 196.0	140.0, 195.6	140.0, 196.0
BMI (kg/m) at Screening				
n	248	1473	308	1413
Mean (SD)	24.82 (5.177)	25.42 (5.162)	24.98 (5.315)	25.41 (5.133)
Median	23.44	24.51	23.53	24.53
Min, max	18.5, 47.9	14.6, 52.9	18.5, 47.9	14.6, 52.9
Smoking status, n(%)				
Former smoker	80 (32.3)	430 (29.2)	94 (30.5)	416 (29.4)
Pack years smoked				
n	72	408	79	401
Mean (SD)	19.1044 (23.0824)	16.6026 (20.9694)	19.1885 (23.0972)	16.5423 (20.9227)
Median	9.2895	9.9973	9.3299	9.9959
Min, max	0.0080, 93.9959	0.0009, 143.9890	0.0080, 93.9959	0.0009, 143.9890
Never smoked	168 (67.7)	1043 (70.8)	214 (69.5)	997 (70.6)
Current smoker	0	0	0	0

Source: Adapted from Table IR-05-1 in IR response submitted on February 10, 2025.
Abbreviations: BMI, Body Mass Index; ITT, Intent-to-Treat; Min, Minimum; Max, Maximum; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; SD, Standard deviation

Table 103 shows the demographic characteristics for the ITT population. The subjects with non-missing data are generally comparable to the overall population in terms of median age, sex, race, ethnicity, height, BMI, smoking status, and world stratification region (refer to Table 9 in Section 6.2.2.4). Overall, the differences between those with missing and non-missing PGIS/PGIC scores are minimal, not clinically significant, and unlikely to affect the interpretation of analyses, particularly given that the demographic characteristics of those with non-missing data generally approximate the overall population.

Table 104 shows the baseline characteristics in ITT population.

Table 104. Baseline Characteristics, ITT Population, Study 301

Characteristics	Non-Missing PGIS Score at Baseline and Week 52	Missing PGIS Score at Baseline or Week 52	Non-Missing PGIC Score at Week 52	Missing PGIC Score at Week 52
PEx in prior 12 months, n(%)				
<3	172 (69.4)	1047 (71.1)	203 (65.9)	1016 (71.9)
≥3	76 (30.6)	426 (28.9)	105 (34.1)	397 (28.1)
Pseudomonas aeruginosa in sputum, n(%)				
Positive	88 (35.5)	519 (35.2)	102 (33.1)	505 (35.7)
Negative	160 (64.5)	954 (64.8)	206 (66.9)	908 (64.3)
Hospitalized in prior 24 months for PEx, n(%)	69 (27.8)	352 (23.9)	84 (27.3)	337 (23.8)
FEV1, pre-bronchodilator (% predicted)				
n	248	1471	308	1411
Mean (SD)	71.8 (22.80)	70.0 (23.28)	71.0 (22.54)	70.0 (23.37)
Median	71.0	69.0	70.0	70.0
Min, max	26, 139	16, 158	26, 139	16, 158
FEV1, post-bronchodilator (L)				
n	248	1465	306	1407
Mean (SD)	1.9652 (0.7702)	1.9466 (0.7978)	1.9626 (0.7719)	1.9464 (0.7986)
Median	1.8260	1.8210	1.8195	1.8210
Min, max	0.593, 4.747	0.540, 5.467	0.593, 4.747	0.540, 5.467
FEV1, post-bronchodilator (% predicted)				
n	248	1465	306	1407
Mean (SD)	75.8 (23.12)	73.1 (23.48)	74.8 (22.76)	73.2 (23.59)
Median	76.0	73.0	74.0	74.0
Min, max	27, 146	22, 156	27, 146	22, 156
FEV1 (% predicted) <50%, post-bronchodilator, n(%)				
Yes	36 (14.5)	265 (18.0)	48 (15.6)	253 (17.9)
No	212 (85.5)	1200 (81.5)	258 (83.8)	1154 (81.7)
Missing	0	8 (0.5)	2 (0.6)	6 (0.4)

Characteristics	Non-Missing PGIS Score at Baseline and Week 52	Missing PGIS Score at Baseline or Week 52	Non-Missing PGIC Score at Week 52	Missing PGIC Score at Week 52
Post-BD FEV1 (% predicted), n(%)				
>80%	100 (40.3)	562 (38.2)	118 (38.3)	544 (38.5)
50-80%	112 (45.2)	638 (43.3)	140 (45.5)	610 (43.2)
30-49%	35 (14.1)	256 (17.4)	47 (15.3)	244 (17.3)
<30%	1 (0.4)	9 (0.6)	1 (0.3)	9 (0.6)
Missing	0	8 (0.5)	2 (0.6)	6 (0.4)
Lung function pattern post-BD spirometry, n(%)				
Obstruction (FEV1/FVC ratio <0.7)	127 (51.2)	729 (49.5)	160 (51.9)	696 (49.3)
PRISm (FEV1<80% and FEV1/FVC ratio ≥0.7)	44 (17.7)	274 (18.6)	54 (17.5)	264 (18.7)
Normal spirometry (FEV1≥80% and FEV1/FVC ratio >0.7)	77 (31.0)	462 (31.4)	92 (29.9)	447 (31.6)
Missing	0	8 (0.5)	2 (0.6)	6 (0.4)
History of COPD, n(%)	21 (8.5)	241 (16.4)	27 (8.8)	235 (16.6)
History of asthma, n(%)	51 (20.6)	270 (18.3)	64 (20.8)	257 (18.2)
Eosinophil count, n(%)				
<300/mm^3	199 (80.2)	1179 (80.0)	247 (80.2)	1131 (80.0)
≥300/mm^3	49 (19.8)	283 (19.2)	61 (19.8)	271 (19.2)
Missing	0	11 (0.7)	0	11 (0.8)
Use of inhaled steroids, n(%)	139 (56.0)	861 (58.5)	170 (55.2)	830 (58.7)
Chronic use of antibiotics, n(%)				
Number of participants taking antibiotics	89 (35.9)	344 (23.4)	109 (35.4)	324 (22.9)
Macrolides	73 (29.4)	256 (17.4)	84 (27.3)	245 (17.3)
Inhaled	23 (9.3)	94 (6.4)	34 (11.0)	83 (5.9)
Other	10 (4.0)	43 (2.9)	12 (3.9)	41 (2.9)
Number of participants not taking antibiotics	159 (64.1)	1129 (76.6)	199 (64.6)	1089 (77.1)
BSI score				
n	248	1465	306	1407
Mean (SD)	7.4 (3.58)	7.1 (3.57)	7.3 (3.60)	7.1 (3.57)
Median	7.0	7.0	7.0	7.0
Min, max	1, 17	1, 20	1, 17	1, 20

Characteristics	Non-Missing PGIS Score at Baseline and Week 52	Missing PGIS Score at Baseline or Week 52	Non-Missing PGIC Score at Week 52	Missing PGIC Score at Week 52
BSI score categories, n(%)				
≤4	57 (23.0)	377 (25.6)	73 (23.7)	361 (25.5)
5-8	104 (41.9)	630 (42.8)	126 (40.9)	608 (43.0)
≥9	87 (35.1)	458 (31.1)	107 (34.7)	438 (31.0)
Missing	0	8 (0.5)	2 (0.6)	6 (0.4)
QoL-B respiratory symptoms domain score (adults)				
n	243	1229	276	1196
Mean (SD)	62.36 (17.090)	60.25 (16.985)	62.27 (17.043)	60.21 (16.992)
Median	62.96	59.26	62.96	59.26
Min, max	14.8, 100.0	3.7, 100.0	14.8, 100.0	3.7, 100.0

Source: Adapted from Table IR-05-2 in IR response submitted on February 21, 2025.
Abbreviations: BD, Bronchodilator; BSI, Bronchiectasis Severity Index; COPD, Chronic obstructive pulmonary disease; CT, Computed Tomography; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; ITT, intent-to-treat; Min, Minimum; Max, Maximum; MRC, Medical Research Council; PEx, Pulmonary Exacerbation; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; PRISm, Preserved ratio impaired spirometry; QoL-B, Quality of Life Questionnaire-Bronchiectasis; SD, Standard deviation

Table 104 shows the disease characteristics for the ITT population. Baseline characteristics of subjects with non-missing data are generally comparable to the overall population in terms of number of PExs in the last year, *P. aeruginosa* status, post-BD FEV1, use of inhaled steroids, and blood eosinophil count (refer to Table 9 in Section 6.2.2.4). Subjects with non-missing data had a higher proportion (10%) of chronic antibiotic users, specifically macrolide users, compared to the overall population as well as a slightly higher proportion of subjects (5%) with severe NCFB defined as a BSI score ≥9. These differences are small, and their clinical meaningfulness is unclear. Given that the baseline disease characteristics of those with non-missing PGIS/PGIC generally approximate the overall population, these small differences are unlikely to impact the interpretation of analyses with PGIS/PGIC.

Table 105 shows the distribution of QOL-B RSS at baseline in the full sample and subsamples. While mean and median QOL-B RSS tend to be somewhat smaller in the anchor subgroup than in the full sample, the difference is not substantial.

Table 105. Distribution of QOL-B RSS at Baseline of Subsamples With and Without PGIS/PGIC, ITT Population, Study 301

Parameter	Full Sample	Non-Missing PGIS Scores at Baseline and Week 52 and/or Non-Missing PGIC Score at Week 52 (i.e., Anchor Subsample)	Missing PGIS From Baseline at Week 52 (i.e., PGIS Anchor Subsample)	Missing PGIC at Week 52 (i.e., PGIC Anchor Subsample)
N	1472	267	1229	1196
Mean (SD)	60.6 (17.0)	61.8 (17.0)	60.3 (17.0)	60.2 (17.0)
Min	3.7	14.8	3.7	3.7
10th percentile	37.0	37.0	37.0	37.0
25th percentile	48.1	51.9	48.1	48.1
Median (50th percentile)	63.0	63.0	59.3	59.3
75th percentile	74.1	74.1	74.1	72.5
90th percentile	81.5	85.2	81.5	81.5
Max	100.0	100.0	100.0	100.0

Source: Adapted from Table A-3 in IR response submitted on February 10, 2025. Results replicated by PFSS reviewer.
Abbreviations: ITT, intent-to-treat; PFSS, patient-focused statistical scientists; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, respiratory symptoms

Table 106 shows the distribution of change from baseline at Week 52 in QOL-B RSS in the full sample and subsamples. The mean and median change scores for the anchor subsamples tended to be larger than those of the full sample indicating this subgroup may have experienced more change in respiratory symptoms than the full sample.

Table 106. Distribution of Change From Baseline at Week 52 in QOL-B RSS of Subsamples With and Without PGIS/PGIC, ITT Population, Study 301

Parameter	Full Sample	Non-Missing PGIS Scores at Baseline and Week 52 and/or Non-Missing PGIC Score at Week 52 (i.e., Anchor Subsample)	Missing PGIS From Baseline at Week 52 (i.e., PGIS Anchor Subsample)	Missing PGIC at Week 52 (i.e., PGIC Anchor Subsample)
N	1107	267	871	847
Mean (SD)	7.5 (17.6)	6.4 (15.4)	7.7 (18.1)	7.8 (18.2)
Min	-66.7	-29.6	-66.7	-66.7
10th percentile	-14.8	-11.1	-14.8	-14.8
25th percentile	-3.7	-3.7	-3.7	-3.7
Median (50th percentile)	7.4	3.7	7.4	7.4
75th percentile	18.5	14.8	18.5	18.5
90th percentile	29.6	22.2	29.6	33.3
Max	77.8	77.8	77.8	77.8

Source: Adapted from Table A-3 in IR response submitted on February 10, 2025. Results replicated by PFSS reviewer.
Abbreviations: ITT, intent-to-treat; PFSS, patient-focused statistical scientists; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, respiratory symptoms

Patient characteristics across the subsamples indicated the groups were comparable.

16.1.4.4. Correlations Between Anchor Assessments and QOL-B RSS, Study 301

The Applicant provided correlations of change from baseline to Week 52 between the QOL-B RSS and anchor measures (i.e., PGIS, PGIC). Moderate correlations were observed between the endpoint score and change in PGIS and PGIC (see Table 107), suggesting PGIS and PGIC may be informative to aid in the interpretation of the change from baseline in QOL-B RSS at Week 52.

Table 107. Correlations of Change From Baseline at Week 52 Between QOL-B RSS and Anchor Measures in ITT Population, Study 301

Change From Baseline to Week 52	Correlation Type	Correlation With Change in Anchor Measure	
		PGIS	PGIC[1]
QOL-B RSS	Pearson correlation	-0.51	-0.40
	Spearman correlation	-0.48	-0.43

Source: Adapted from Table B-4 in Study 301 Psychometric Report Memo (RTI-HS Project No. 0307201) and Table A-6.a. in IR response submitted on February 10, 2025. Results replicated by PFSS reviewer.
[1] PGIC was not measured at baseline as the item asked patients to report "the overall status since the start of the study." The correlations are between change from baseline at Week 52 in QOL-B RSS and PGIC at Week 52.
Abbreviations: ITT, intent-to-treat; PFSS, patient-focused statistical scientists; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, respiratory symptoms

16.1.4.5. Target Anchor Change Category, Study 301

The Applicant prespecified a one-category improvement in PGIS as the primary target anchor change category representing a clinically meaningful improvement to patients. Additionally, the "minimally improved" and "much improved" categories in PGIC were considered supportive. The Applicant did not provide evidence from patient input to demonstrate the proposed target change categories on the anchor scales. However, the review team determined a 1-category improvement on the PGIS appears to be a reasonable target anchor change category. Given the uncertainty regarding what category change on the seven-point PGIC constitutes a clinically meaningful improvement or worsening, the review team examined anchor-based analysis results based on both the "minimally improved" and "much improved" categories on the PGIC as target anchor changes.

A 1-category improvement on the PGIS anchor scale could occur in the following ways:

- Change from "Very Severe" to "Severe"
- Change from "Severe" to "Moderate"
- Change from "Moderate" to "Mild"
- Change from "Mild" to "None"

Table 108 shows the change in the PGIS from baseline at Week 52 by baseline PGIS. The majority of subjects reported "Mild" or "Moderate" symptoms at Baseline. For those subjects, most experienced either a 1-point improvement (23.01%) or "no change" (32.5%) in overall severity at Week 52. Of note, the percentages in Table 108 are calculated relative to the PGIS anchor subsample, which had a sample size of 243.

Table 108. PGIS: Change From Baseline at Week 52 Summarized by Baseline Severity, PGIS Anchor Subsample, Study 301

Parameter		PGIS at Baseline				
Change in PGIS From Baseline at Week 52	None	Mild	Moderate	Severe	Very Severe	N (%*)
N (%*)	45 (18.52%)	74 (30.45%)	105 (43.21%)	17 (7.00%)	2 (0.82%)	243 (100.00%)
4-point improvement	0	0	0	1 (0.41%)	0	1 (0.41%)
3-point improvement	0	0	0	0	0	0
2-point improvement	0	0	9 (3.70%)	6 (2.47%)	1 (0.41%)	16 (6.58%)
1-point improvement	0	18 (7.41%)	38 (15.60%)	8 (3.29%)	0	64 (26.34%)
No change	27 (11.10%)	28 (11.50%)	51 (21.00%)	1 (0.41%)	0	107 (44.03%)
1-point worsening	10 (4.12%)	26 (10.70%)	7 (2.88%)	2 (0.82%)	0	45 (18.52%)

Parameter		PGIS at Baseline				
Change in PGIS From Baseline at Week 52	None	Mild	Moderate	Severe	Very Severe	N (%*)
2-point worsening	7 (2.88%)	2 (0.82%)	0	0	0	9 (3.70%)
3-point worsening	1 (0.41%)	0	0	0	0	1 (0.41%)
4-point worsening	0	0	0	0	0	0

Source: Results created by PFSS reviewer.
* Noted by the PFSS reviewer: The percentage in each cell is calculated by sample size divided by the total sample size who have PGIS change scores from baseline at Week 52 and are not missing QOL-B RSS at baseline.
Abbreviations: ITT, Intent-to-Treat; N, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; PGIS, Patient Global Impression of Severity; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, respiratory symptoms

16.1.4.6. Applicant's Anchor-Based Analyses, Study 301

In the original submission, the Applicant conducted anchor-based analyses using PGIS and PGIC as anchor measures to aid in the interpretation of the change from baseline at Week 52 in the QOL-B RSS. The Applicant used the mean change from baseline in the QOL-B RSS at Week 52 in the 1-category improvement PGIS subgroup as the primary clinically meaningful change threshold. Additionally, median changes in the 1-category improvement PGIS subgroup and mean and median changes in the "minimally improved" PGIC subgroup were considered supportive threshold estimates. Based on the conducted meaningful change analyses, the Applicant concluded that an improvement in QOL-B RSS in the range of 11 to 14 is meaningful.

Given the limitations of using PGIS and PGIC as anchor measures (see Section 16.1.4.2), the Agency sent an information request on January 29, 2025, for supplemental anchor-based meaningful change analysis using the UA item to aid in the interpretation of the QOL-B-RSS-based endpoint results. In the Applicant's February 10, 2025, response, the Applicant stated they used the same approach described above, to derive meaningful within-patient improvement values by triangulating the results from the following:

- Anchor-based analyses supplemented by eCDF curves and probability density function curves using the following anchor measures:
  - PGIS
  - PGIC
  - UA item
- Supplemental analyses using baseline PGIS. Specifically,
  - Mean and median QOL-B RSS domain change scores for patients with a 1-point PGIS improvement and a baseline PGIS of "Mild"
  - Mean and median QOL-B RSS domain change scores for patients with a 1-point PGIS improvement and a baseline PGIS of "Moderate."
- Based on the original analyses and the additional analyses conducted in response to the Agency's information request, the Applicant concluded that the final meaningful change threshold remains unchanged from the originally proposed range of 11 to 14.

16.1.4.7. Agency's Anchor-Based Analyses, Study 301

In order to understand the amount of improvement in QOL-B RSS that is considered meaningful to subjects, it is helpful first to examine the distribution of baseline scores by treatment arm (Table 109). Overall, baseline QOL-B RSS were similar between arms in Study 301.

Table 109. Distribution of Baseline QOL-B RSS by Treatment Arm, ITT Population, Study 301

Treatment	N	Mean (SD)	Median	Min	Max
Brensocatib 10 mg QD	488	59.8 (17.0)	59.3	11.1	100
Brensocatib 25 mg QD	497	61.9 (17.2)	63.0	3.7	100
Placebo	487	60.0 (16.8)	59.3	7.4	96.3

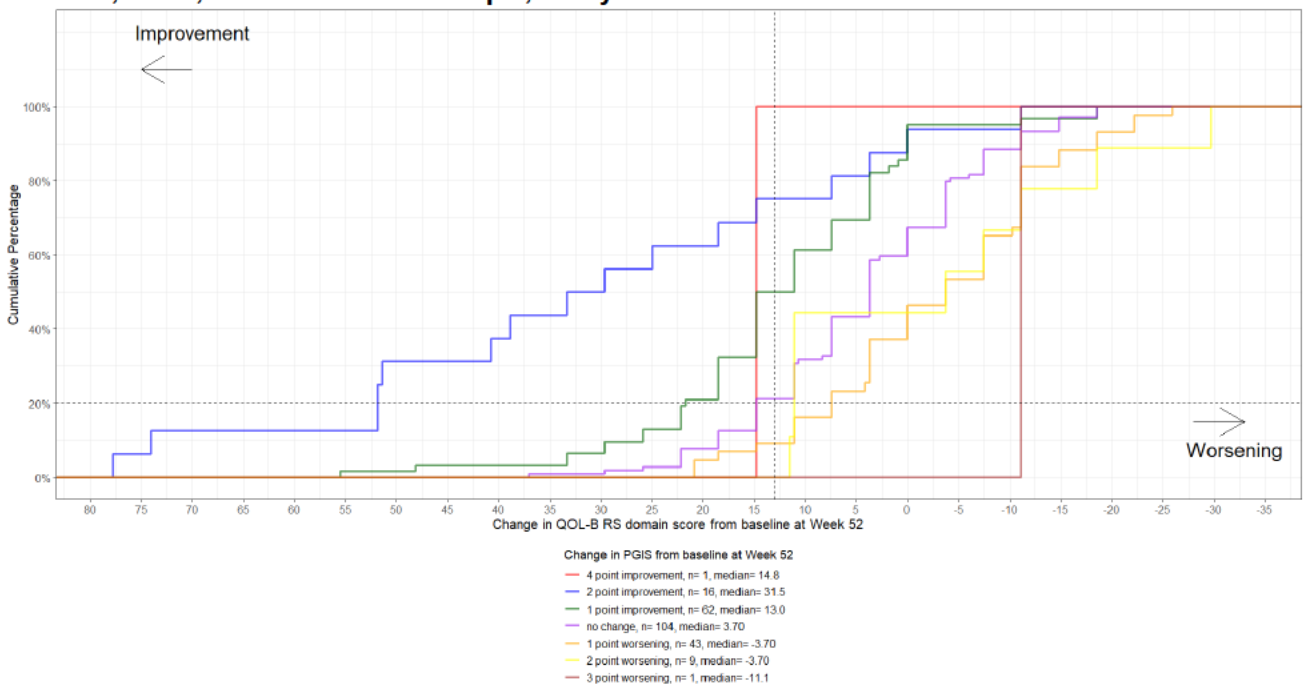
Source: Adapted from Table 10 in Study 301 Clinical Study Report. Results replicated by PFSS reviewer.
Abbreviations: ITT, intent-to-treat; Min, minimum; Max, maximum; N, sample size; PFSS, patient-focused statistical scientists; QD, once daily; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms; SD, standard deviation

The Agency conducted a primary anchor-based analyses using the PGIS and PGIC as anchor variables and a supplemental anchor-based analyses using the UA item. As the results of these analyses were comparable, only the results of the PGIS and PGIC anchor-based analyses are discussed.

Figure 69 and Figure 70 show the eCDF plots of change from baseline in QOL-B RSS at Week 52 by change in PGIS and PGIC, respectively. In these figures, the change in the QOL-B RSS from baseline at Week 52 is plotted on the x-axis. A positive change (>0) represents an improvement in the QOL-B RSS and a negative change (<0) represents a worsening in the score. Because the focus of the anchor-based analysis is to determine the amount of change in QOL-B RSS that would constitute a meaningful improvement for subjects, it is important to note when interpreting these eCDF plots (Figure 69 and Figure 70), the cumulative proportion of subjects reaching a specific threshold is the percentage of patients at a given QOL-B RSS domain change score (y-axis).

As shown in Figure 69, for subjects who experienced a 1-point improvement in PGIS, the median change in QOL-B RSS is 13.0. At 13.0, more than 20% of subjects who experienced no change or worsening (i.e., no change, 1-point worsening, 2-point worsening, and 3-point worsening) on PGIS would be misclassified as having experienced a meaningful improvement in QOL-B RSS. To ensure fewer than 20% of subjects who reported having no change or worsening on the PGIS would be misclassified as having experienced a meaningful improvement in QOL-B RSS, a threshold of 16-point improvement in QOL-B RSS is needed.

Figure 69. Change From Baseline in QOL-B RSS at Week 52 by PGIS Category of Change From Baseline, eCDF, PGIS Anchor Subsample, Study 301

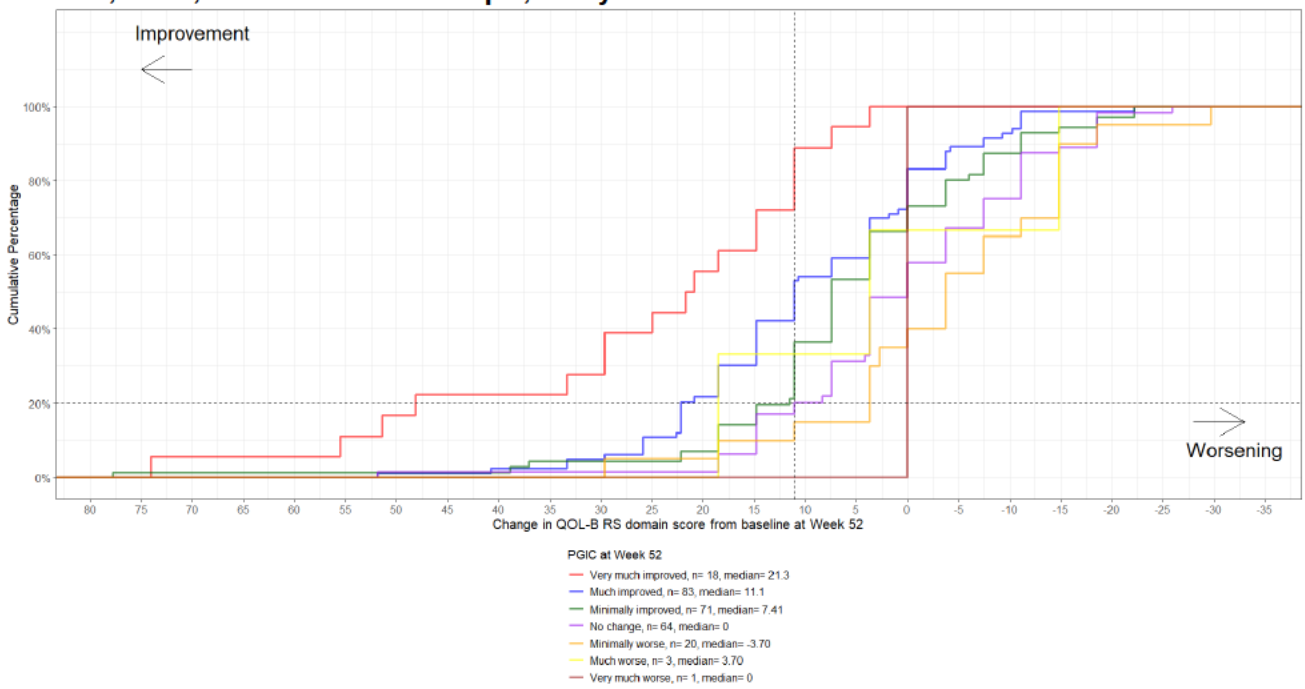


Source: Figure modified from Figure 2 in Study 301 Psychometric Report Memo (RTI-HS Project No. 0307201). Results replicated by PFSS reviewer.
Abbreviations: eCDF, empirical Cumulative Distribution Function; ITT, intent-to-treat; n, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; PGIS, Patient Global Impression of Severity; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms

Figure 70 shows that, for subjects who experienced "minimally improved" in PGIC, the median change in QOL-B RSS is 7.41. At 7.41, more than 20% of subjects who experienced no change or worsening (i.e., no change, minimally worse, much worse, very much worse) on the PGIC would be misclassified as having experienced a meaningful improvement in QOL-B RSS. To ensure fewer than 20% of subjects who reported having no change or worsening on the PGIC would be misclassified as having experienced a meaningful improvement in QOL-B RSS, a threshold of 16-point improvement in QOL-B RSS is needed.

Also evident in Figure 70, for subjects who experienced "much improved" in PGIC, the median change in QOL-B RSS is 11.1. At 11.1, more than 20% of subjects who experienced less improvement, no change or worsening on the PGIC would be misclassified as having experienced a meaningful improvement in QOL-B RSS. To ensure fewer than 20% of subjects who reported having less improvement, no change or worsening on the PGIC would be misclassified as having experienced a meaningful improvement in QOL-B RSS, a threshold of 20-point improvement in QOL-B RSS is needed.

Figure 70. Change From Baseline in QOL-B RSS at Week 52 by PGIC Response Category at Week 52, eCDF, PGIC Anchor Subsample, Study 301



Source: Figure modified from Figure 3 in Study 301 Psychometric Report Memo (RTI-HS Project No. 0307201). Results replicated by PFSS reviewer.
Abbreviations: eCDF, empirical Cumulative Distribution Function; ITT, intent-to-treat; n, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; PGIC, Patient Global Impression of Change; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms

As the amount of change in QOL-B RSS that subjects consider a meaningful improvement may depend on subjects' baseline statuses, the distribution of change in QOL-B RSS was examined by baseline overall severity (i.e., PGIS) Table 110 shows the distribution of change in QOL-B RSS by baseline PGIS for subjects who experienced the target anchor change category of a1-point improvement on PGIS.

Table 110. Distribution of Change in QOL-B RSS From Baseline at Week 52 by Baseline PGIS Among Subjects With 1-Point Improvement in PGIS, PGIS Anchor Subsample, Study 301

Change in QOL-B RSS From Baseline at Week 52	PGIS at Baseline				
	None	Mild	Moderate	Severe	Very Severe
N	0	17	38	7	0
Mean (SD)	-	11.7 (10.5)	14.9 (12.7)	2.6 (16.1)	-
10th percentile	-	3.7	0	-18.5	-
25th percentile	-	3.7	7.4	-18.5	-
Median (50th percentile)	-	11.1	14.8	3.7	-
75th percentile	-	21.8	18.5	18.5	-
90th percentile	-	25.9	33.3	18.5	-

Source: Adapted from Table A-5.d. in IR response submitted on February 10, 2025. Results replicated by PFSS reviewer.
Abbreviations: ITT, intent-to-treat; N, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; PGIS, Patient Global Impression of Severity; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms; SD, standard deviation

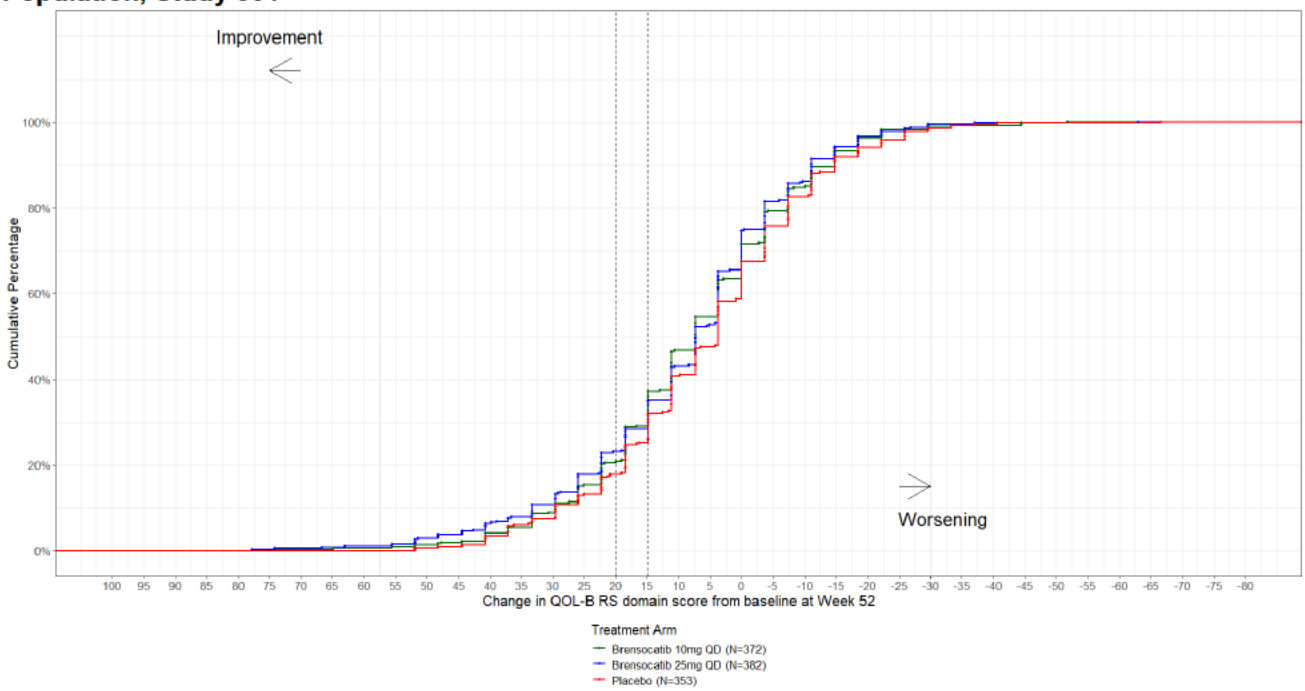
Considering the distribution of change in QOL-B RSS for subjects who experienced a 1-point improvement in PGIS, a14.8-point improvement in QOL-B RSS would be needed to ensure that

at least 50% of subjects who experienced moderate overall severity or slight problems at baseline would be classified as experiencing a meaningful improvement.

Taking into consideration the full distribution of change in QOL-B RSS and subjects' baseline status and selecting meaningful change thresholds that minimize the misclassification of subjects who experienced less improvement, no change or worsening, a plausible range of clinically meaningful change thresholds in QOL-B RSS is between a14.8- to 20-point improvement in Study 301.

Figure 71 shows the eCDF curves for the QOL-B-RSS-endpoint score by treatment arm. Based on visual inspection, there is no clear or consistent separation between the brensocatib 10 mg QD arm and the placebo arm, or between the brensocatib 25 mg QD arm and the placebo arm, through the distribution of endpoint scores.

Figure 71. Change From Baseline at Week 52 in QOL-B RSS by Treatment Arm, eCDF, ITT Population, Study 301



Source: Figure modified from Figure IR-05-1 in IR response submitted on February 10, 2025. Results replicated by PFSS reviewer.
Abbreviations: eCDF, empirical Cumulative Distribution Function; ITT, intent-to-treat; N, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms; QD, once daily

Given the limitations with the available anchor measures (see Section 16.1.4.2), the review team also examined the separation between the eCDF curves within the Agency-determined plausible range of clinically meaningful change thresholds of 14.8 to 20, the Applicants meaningful change range of 11 to 14, and at a score change of 0.

Table 111 shows the percentage of subjects in each trial arm that experienced meaningful improvement in the QOL-B RSS at Week 52 from baseline at various threshold values within as well as outside of the Agency-determined plausible range of clinically meaningful change thresholds (14.8- to 20-point improvement). At the threshold of 14.8-point improvement, the differences in response rates between the brensocatib 10 mg QD arm and the placebo arm and

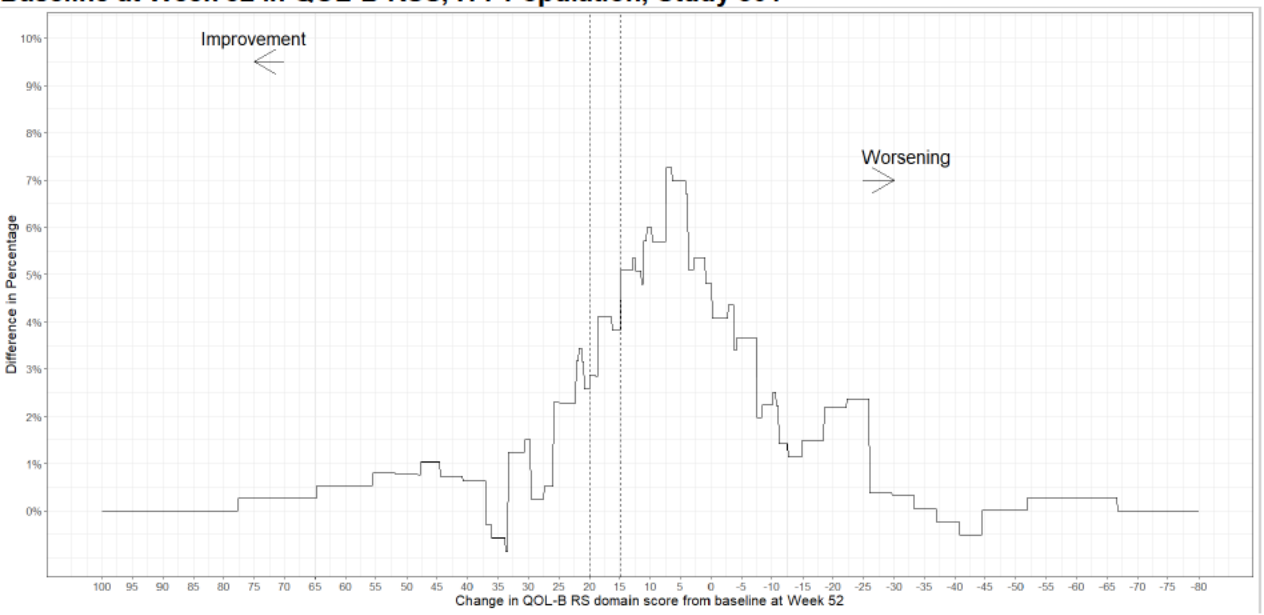
between the brensocatib 25 mg QD arm and the placebo arm are 5.1% and 3.1%, respectively. In addition, at the threshold of 20-point improvement, the differences in response rates between the brensocatib 10 mg QD arm and the placebo arm and between the brensocatib 25 mg QD arm and the placebo arm are 2.6% and 5.2%, respectively.

Table 111. Percentage of Subjects Who Experienced Improvement in QOL-B RSS at Week 52 From Baseline at Various Thresholds, ITT Population, Study 301

Threshold	Percentage of Subjects in Brensocatib 10 mg QD Group (%)	Percentage of Subjects in Brensocatib 25 mg QD Group (%)	Percentage of Subjects in Placebo Group (%)	Difference in Percentage Between Brensocatib 10 mg QD and Placebo Groups (%)	Difference in Percentage Between Brensocatib 25 mg QD and Placebo Groups (%)
≥0	63.4%	65.4%	58.6%	4.8%	6.8%
≥11	46.5%	42.7%	40.8%	5.7%	1.9%
≥14*	37.1%	35.1%	32.0%	5.1%	3.1%
≥14.8	37.1%	35.1%	32.0%	5.1%	3.1%
≥20	20.4%	23.0%	17.8%	2.6%	5.2%

Source: Table generated by PFSS reviewer.
*Noted by the PFSS reviewer: The QOL-B RSS was transformed to a 0-100 scale. Of note, transformed scores of 14 and 14.8 represent the same original value.
Abbreviations: eCDF, empirical Cumulative Distribution Function; ITT, intent-to-treat; N, number of subjects with given characteristic; PFSS, patient-focused statistical scientists; QD, once daily; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms

Figure 72. eCDF Difference Between Brensocatib 10 mg QD and Placebo Across Change From Baseline at Week 52 in QOL-B RSS, ITT Population, Study 301

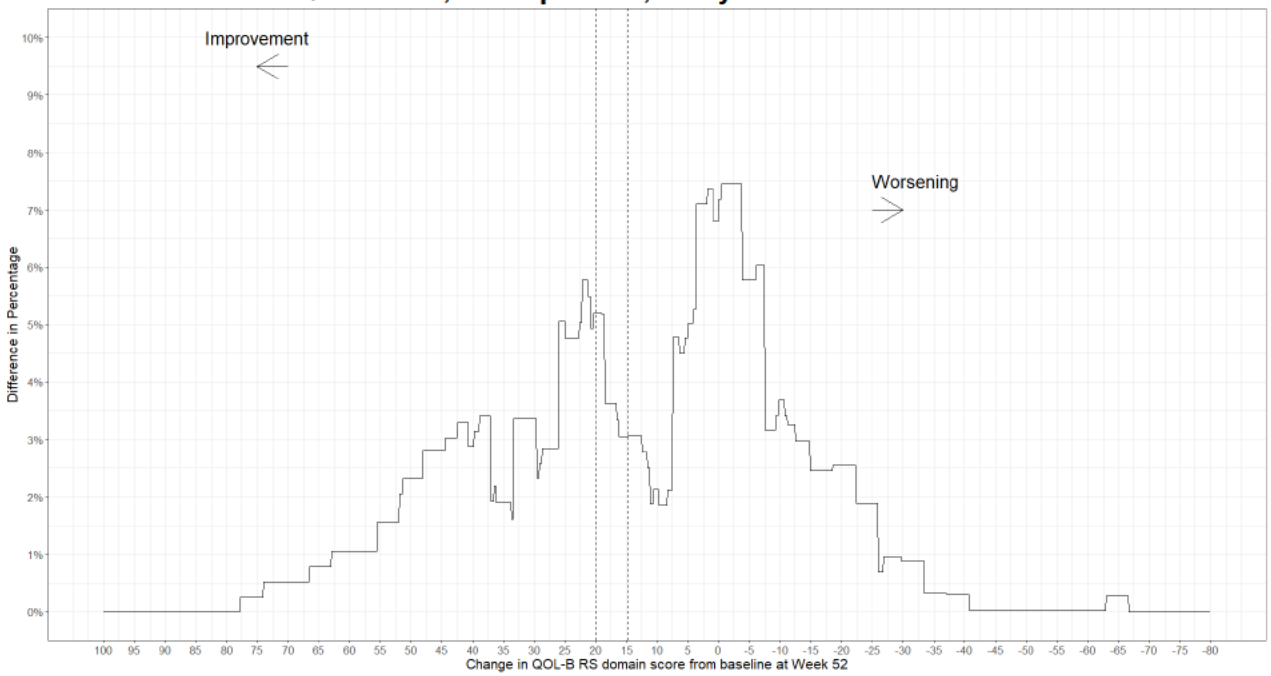


Source: Figure generated by PFSS reviewer.
Abbreviations: ITT, Intent-to-Treat; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms; eCDF, empirical Cumulative Distribution Function; N, number of subjects with given characteristic; QD, once daily; PFSS, patient-focused statistical scientists

For easier visualization, Figure 72 and Figure 73 show the eCDF difference curves between brensocatib 10 mg QD and placebo (i.e., brensocatib 10 mg QD - placebo) and between

brensocatib 25 mg QD and placebo (i.e., brensocatib 25 mg QD - placebo), respectively, across change from baseline at Week 52 in QOL-B RSS. In Figure 72, within the Agency-determined range of 14.8- to 20-point improvement in QOL-B RSS, the differences in response rates between the brensocatib 10 mg QD arm and the placebo arm are between 2.6% and 5.1%. In Figure 73, within the Agency-determined range of 14.8- to 20-point improvement in QOL-B RSS, the differences in response rates between the brensocatib 25 mg QD arm and the placebo arm are between 3.1% and 5.2%.

Figure 73. eCDF Difference Between Brensocatib 25 mg QD and Placebo Across Change From Baseline at Week 52 in QOL-B RSS, ITT Population, Study 301



Source: Figure generated by PFSS reviewer.
Abbreviations: ITT, Intent-to-Treat; QOL-B, Quality of Life Questionnaire–Bronchiectasis; RSS, Respiratory Symptoms; eCDF, empirical Cumulative Distribution Function; N, number of subjects with given characteristic; QD, once daily; PFSS, patient-focused statistical scientists

16.1.4.8. Conclusion, Study 301

Based on the results of the Agency's anchor-based analyses, which incorporate the subjects' perspectives, there is no evidence that the observed improvement in subjects with NCFB when treated with brensocatib 10 mg QD and brensocatib 25 mg QD, as assessed by the endpoint of change from baseline at Week 52 in QOL-B RSS, is representative of a clinically meaningful improvement in Study 301. Therefore, QOL-B RSS data could not be communicated in labeling in a way that would be informative and not misleading, see Section 6.3.3 and Section 23 for further discussion.

16.2. Study 201

16.2.1. Sensitivity and Supplementary Analyses, Study 201

The supplementary analysis of the time to first PEx for the per-protocol population is summarized in Table 112. The results were consistent with and supportive of the primary analysis.

Table 112. Sensitivity Analysis: Time to First Pulmonary Exacerbation Through Week 24 in PP Analysis Set, Study 201

Parameter	Brensocatib 10 mg QD N=65	Brensocatib 25 mg QD N=67	Placebo N=64
Subjects with PExs, n(%)	24 (36.9)	26 (38.8)	34 (53.1)
Median time to first PEx in days[1] (95% CI)	NE (NE, NE)	NE (183, NE)	177 (101, NE)
One-sided p-value	0.03	0.06	-

Source: Clinical Study Report Table and Figures, Table 14.2.1.1.2.1; findings reproduced by the statistical reviewer using adtte.xpt
[1] Kaplan Meier estimates were used for the median time to first PEx. Confidence intervals are two-sided 95% confidence intervals.
[2] The stratified log-rank test was used to estimate a one-sided p-value, stratified by sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit and maintenance antibiotic use at baseline.
Abbreviations: CI, confidence interval; NE, not estimable; PEx, pulmonary exacerbation; PP, per-protocol; QD, once daily

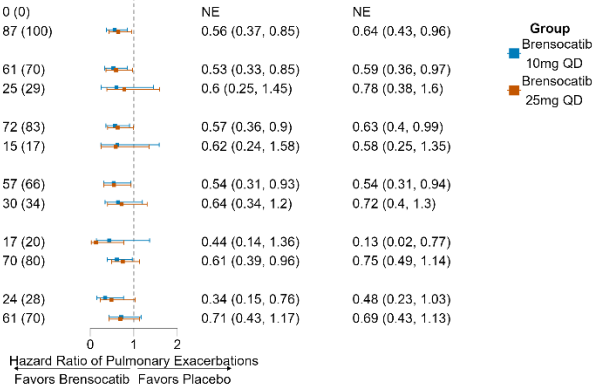
Results from the sensitivity analysis with a stratified Cox proportional hazards model were consistent with the primary analysis. Point estimates and 95% confidence intervals for the overall population are depicted in the forest plot in Figure 74. The one-sided p-value compared to placebo for the brensocatib 10-mg group was 0.01 and for the brensocatib 25-mg group was 0.02. These results were supportive of the primary analysis.

Subgroup Analyses

The Forest plot in Figure 74 summarizes the results of the subgroup analyses of the time to first PEx for Study 201 based on a stratified Cox proportional hazards model. The results based on an unstratified Cox proportional hazards model were similar. Results were consistent with the overall analysis across the prespecified subgroups as well as post hoc subgroups for sex, race, and ethnicity.

Figure 74. Subgroup Analysis: Forest Plot of Time to First Pulmonary Exacerbation With Stratified Cox Proportional Hazards Model in ITT Analysis Set, Study 201

Variable	Brensocatib 10mg QD, n (%)	Brensocatib 25mg QD, n (%)	Placebo, n (%)	Hazard Ratio (95% CI) for 10mg arm	Hazard Ratio (95% CI) for 25mg arm
Overall	82 (100)	87 (100)	87 (100)	0.58 (0.38, 0.87)	0.62 (0.41, 0.92)
Age Group					
< 65 Years	34 (41)	39 (45)	33 (38)	0.89 (0.43, 1.82)	1.03 (0.53, 2)
>=65 Years	48 (59)	48 (55)	54 (62)	0.48 (0.29, 0.8)	0.5 (0.3, 0.84)
Sex					
Female	57 (70)	62 (71)	55 (63)	0.46 (0.27, 0.78)	0.64 (0.4, 1.03)
Male	25 (30)	25 (29)	32 (37)	0.9 (0.46, 1.77)	0.54 (0.24, 1.18)
Race					
African American / Black People Of African Origin	0 (0)	2 (2)	2 (2)	NE	NE
Asian	5 (6)	5 (6)	13 (15)	NE	0.84 (0.11, 6.49)
Caucasian (White)	76 (93)	78 (90)	71 (82)	0.52 (0.34, 0.79)	0.53 (0.35, 0.81)
Native Hawaiian Or Other Pacific Islander	1 (1)	1 (1)	1 (1)	NE	NE
Ethnicity					
Hispanic Or Latino	2 (2)	4 (5)	0 (0)	NE	NE
Not Hispanic Or Latino	80 (98)	83 (95)	87 (100)	0.56 (0.37, 0.85)	0.64 (0.43, 0.96)
Baseline Pulmonary Exacerbations					
0-2	59 (72)	51 (59)	61 (70)	0.53 (0.33, 0.85)	0.59 (0.36, 0.97)
3 Or More	23 (28)	36 (41)	25 (29)	0.6 (0.25, 1.45)	0.78 (0.38, 1.6)
Maintenance Use Of Macrolides At Baseline					
No	69 (84)	71 (82)	72 (83)	0.57 (0.36, 0.9)	0.63 (0.4, 0.99)
Yes	13 (16)	16 (18)	15 (17)	0.62 (0.24, 1.58)	0.58 (0.25, 1.35)
Pa Colonization At Baseline					
Negative	54 (66)	54 (62)	57 (66)	0.54 (0.31, 0.93)	0.54 (0.31, 0.94)
Positive	28 (34)	33 (38)	30 (34)	0.64 (0.34, 1.2)	0.72 (0.4, 1.3)
Pooled BSI Group					
< 5	18 (22)	18 (21)	17 (20)	0.44 (0.14, 1.36)	0.13 (0.02, 0.77)
>= 5	64 (78)	69 (79)	70 (80)	0.61 (0.39, 0.96)	0.75 (0.49, 1.14)
Baseline FEV1 % predicted post-bronchodilator					
FEV1 (% Predicted) < 50%	23 (28)	18 (21)	24 (28)	0.34 (0.15, 0.76)	0.48 (0.23, 1.03)
FEV1 (% Predicted) >= 50%	59 (72)	69 (79)	61 (70)	0.71 (0.43, 1.17)	0.69 (0.43, 1.13)



Source: Statistical Reviewer Analysis; adtte.xpt and adsl.xpt
Abbreviations: BSI, bronchiectasis severity index; FEV1 forced expiratory volume in 1 second; ITT, intent-to-treat; Pa, *Pseudomonas aeruginosa*; NE, not estimable; QD, once daily

16.2.2. Secondary Endpoints, Study 201

The least square mean change from screening in post-BD ppFEV1 at Week 24 was −0.33 (95% CI = -2.07, 1.41) for the brensocatib 10-mg group, −0.30 (95% CI = -1.98, 1.38) for the brensocatib 25-mg group and −1.79 (95% CI = -3.49, −0.08) for the placebo group. The estimated least square mean differences between treatment groups compared to placebo were 1.46 (95% CI = -0.70, 3.62) for the brensocatib 10-mg group and 1.49 (95% CI = -0.67, 3.64) for the brensocatib 25-mg group. Based on the post hoc sensitivity analysis, the estimated least square mean differences compared to placebo were 1.42 (95% CI = -0.73, 3.58) for the brensocatib 10-mg group and 1.77 (95% CI = -0.50, 4.04) for the brensocatib 25-mg group. Results from the sensitivity analysis were consistent with the primary analysis of this endpoint.

More subjects experienced at least one pulmonary exacerbation during the 24-week treatment period in the placebo group (42, 48.3%) than in the brensocatib groups (26, 31.7% for 10 mg; 29, 33.3% for 25 mg). Analyses based on the stratified Cochran-Mantel-Haenszel test assume that all subjects for whom a PEx was not observed, including during time subjects have missing data, were exacerbation-free, thus likely overestimating the number of responders. The sensitivity analyses using unadjusted and covariate-adjusted negative binomial models demonstrated treatment effects that favored both brensocatib arms compared to placebo (unadjusted, 10 mg versus placebo: 0.64, 95% CI =0.42, 0.99; unadjusted, 25 mg versus placebo: 0.77, 95% CI =0.52, 1.15; adjusted, 10 mg versus placebo: 0.64, 95% CI =0.42, 0.98; adjusted, 25 mg versus placebo: 0.75, 95% CI =0.50, 1.13). Although analyses for secondary endpoints in Study 201 were not controlled for multiplicity with the same rigor as in Study 301, the numeric trends

observed are consistent with results from Study 301 and provide additional support for the effectiveness of brensocatib 10- and 25-mg doses.

In Study 201, the change from baseline in QoL-B respiratory symptoms score over the 24-week treatment period was not statistically significant or clinically meaningful for the comparisons between both brensocatib arms and placebo.

17. Clinical Safety

Electrocardiograms

No clinically significant ECG trends or safety concerns were identified in Study 301 or Study 201.

QT

Brensocatib did not prolong the QTcF interval in the thorough QT study assessment (INS1007-104). This was reviewed by the Interdisciplinary Review Team for Cardiac Safety Studies in their review memo dated February 20, 2024.

Additional Skin-related Safety Analyses

The DDD consult team recommended analyzing skin-related TEAEs by grouping of preferred terms based on expert knowledge of the clinical presentation and pathophysiology of these entities to ensure a more accurate assessment of skin-related events in Studies 301 and 201. For full details, see DDD Consult memo dated February 7, 2025.

Table 113 displays the preferred term groupings used for the assessment of skin-related events. The primary clinical reviewer reviewed all subject narratives, medical history, vital signs, and concomitant medications to verify whether the individual AE should be included in the grouped query analyses as defined in the legend to Table 113.

Table 113. Grouping of Preferred Terms for Assessment of Skin-Related TEAEs

TEAE	Group of Preferred Terms
Rash [inflammatory]	• Rash • Rash maculopapular • Rash pruritic • Rash papular • Rash erythematous • Rash exfoliative[1] • Dermatitis • Erythema • Miliaria[2,3]
Dry skin	• Skin exfoliation • Xerosis • Skin fissures • Xeroderma • Cheilitis

TEAE	Group of Preferred Terms
	• Lip dry • Chapped lips
Eczema	• Dermatitis atopic • Eczema asteatotic • Hand dermatitis[1] • 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[2,4] • Swelling of eyelid[2,4] • Swelling face[4] • Lip pruritus[2,4]
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[3]
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

TEAE	Group of Preferred Terms
	• Sweat gland tumor
Pruritus	• Ear pruritus • Vulvovaginal pruritus • Prurigo
Abnormal skin sensation	• Paresthesia • Burning sensation • Pain of skin • Sensitive skin • Hypoesthesia • Hyperesthesia • Tenderness • Skin irritation
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

TEAE	Group of Preferred Terms
	• Skin infection • Ear lobe infection
Alopecia	• Diffuse alopecia • Hair growth abnormal[2,3] • Hair texture abnormal[3]
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 hyperemia • Oral pain • Oral discomfort • Mouth swelling • Paresthesia oral • Oropharyngeal discomfort • Hypoesthesia oral • Oral mucosal erythema
Dry mouth	• Salivary gland cyst • Salivary gland disorder • Salivary gland enlargement • Benign salivary gland neoplasm

TEAE	Group of Preferred Terms
Oral candidiasis	• Oral herpes • Herpangina • Oral fungal infection • Oropharyngeal candidiasis

Source: Clinical Data Scientist extrapolated from DDD consult memo dated February 20, 2024.
[1] indicates a preferred terms is a non-specific and verbatim term requiring narrative review for verification of inclusion in grouping.
[2] preferred terms excluded per clinical review
[3] Terms in italics may be considered for inclusion in a grouping upon individual AE review verbatim terms/narratives for confirmation.
[4] indicates a preferred term that is a manifestation of a hypersensitivity reaction and requires individual AE assessment with verbatim terms/narratives to confirm appropriate groupings.

120-Day Safety Update

The Applicant submitted a 120-day safety update consisting of final safety data from all subjects in Study 301, including the 122 subjects (20 adolescents on treatment, 99 adults and 3 adolescents in the follow-up period) who were ongoing in the study at the primary data cutoff date. The safety update also includes additional supportive data from the completed phase 1 Study INS1007-110 in healthy subjects and from 3 ongoing studies through the data cutoff date of January 11, 2025: the phase 2 Study INS1007-221 (BiRCh, in subjects with chronic rhinosinusitis with nasal polyps), the phase 2 Study INS1007-231 (CEDAR, subjects with hidradenitis suppurativa), and the expanded access program offered to subjects who have completed either Study 301 or Study 201.

There were no deaths or TEAEs leading to treatment or study discontinuation in the safety update for Study 301. Review of the additional 22 TEAEs occurring in 13 subjects after primary database lock were mostly mild (14/22), and reported PTs were generally consistent with the safety data from the overall population. There were two SAEs that occurred after primary database lock in the 10-mg group involving a bronchiectasis exacerbation in an adolescent and dengue fever in an adult in the follow-up treatment period. Neither of these appear to be related to study treatment. There was also one TEAE of mild urticaria in a 13-year-old male in the 25-mg group. No meaningful trends were observed among the hematologic or chemistry laboratory tests, vital signs, or ECG evaluations, and there were no new cases of Hy's law or potential Hy's law. Overall, the safety update did not reveal any new information to alter the conclusions on brensocatib safety profile.

18. Clinical Virology

This section is not applicable to the review of brensocatib tablets.

19. Clinical Microbiology

This section is not applicable to the review of brensocatib tablets.

20. Mechanism of Action/Drug Resistance

For Mechanism of Action Refer to Sections 5.1 and 13.1.1. Drug resistance data is not applicable to this review.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

An Office of Scientific Investigation consult evaluated four trial sites comprising two sites from each trial. Sites were selected based on high enrollment, efficacy outcomes, and safety. The sites chosen for inspection are shown in Table 114. Based on the inspection results, the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the Applicant are acceptable to support this NDA. See the separately filed Clinical Inspection Summary dated July 9, 2025, for additional information.

Table 114. Office of Scientific Investigation Inspection Sites

Principal Investigator	Address	Trial	Site Number	Number of Subjects
Dr Simon D. Bowler	Mater Misericordia Medical Centre Level 3, Aubigny Place Raymond Terrace South Brisbane, Queensland 4101 Australia	201	AUS002	22
Dr. Barry W. Sigal	Southeastern Research Center 2932 Lyndhurst Avenue Winston-Salem, NC 27103	201	USA037	12
Dr. Maria C. De Salvo	Centro Médico Dra De Salvo- (b) (4) Avenida Cabildo 1548, Piso 1°A Ciudad Autónoma De, Buenosaires C1426ABP Argentina	301	ARG004	49
Dr. Victor H. Cambursano	Instituto De Medicina Respiratoria - Imer Avenida Colon 2057 Hospital Rawson Centro Dr. Lázaro Langer Córdoba, Córdoba, X5003DCE Argentina	301	ARG00	18

Source: Clinical Reviewer

23. Labeling: Key Changes

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 115). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 115. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	Not applicable
1 INDICATIONS AND USAGE	No changes were made to the indication statement: "BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older."
2 DOSAGE AND ADMINISTRATION	(b) (4) (b) (4) The two recommended dosages available for treatment of NCFB are: 10 mg or 25 mg orally once daily with or without food. Dose selection is discussed in Section 6.3.1 of the IRT.
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	Added 5.1 Dermatologic Adverse Reactions in Warnings and Precautions to summarize the breadth of skin-related adverse reactions and to recommend monitoring of skin for new rash or lesions and referral to dermatology for evaluation. This is discussed in Section 7.7 of the IRT. Added 5.2 Gingival and Periodontal Adverse Reactions in Warnings and Precautions, and the recommendations for dental referral, routine dental care, and patient education to conduct routine dental hygiene. This is discussed in Sections 7.6.1.6 and 7.6.2.6 of the IRT. Live Attenuated Vaccines subsection was amended to better convey the unknown (b) (4) to a vaccine.
6 ADVERSE REACTIONS	Section 6.1 was updated as follows: • The entire section (b) (4) display safety data from ASPEN first followed by WILLOW because the safety review relied predominately on ASPEN followed by support from WILLOW given the differences in both population size and treatment duration. This change in organization resulted in the removal of the (b) (4) which was replaced with a table of adverse reactions from Trial ASPEN. • Summary of adverse reactions data from WILLOW was added in text below and includes a description of the increased frequency of gingival and periodontal events in WILLOW. • Updated adverse reactions table to include additional reactions of upper respiratory tract infections (including COVID-19, coronavirus infection, influenza, upper respiratory tract infection, viral infection, and viral upper respiratory tract infection) and hypertension, which were reactions that occurred with greater frequency in the 10-mg group compared to the 25-mg group. • Modified the data of skin-related adverse reactions in the table to reflect data obtained from FDA analyses based DDD's recommended term groupings. This is discussed in Section 7.7.2 of the IRT. • Included additional data on LFTs to inform prescribers of the low risk for drug-induced liver injury and the potential to see a mild, sustained increase in liver transaminases. This is discussed in Section 7.6.1.8 of the IRT.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	• Included additional data on skin cancers and alopecia to inform prescribers of these rarer, dose-dependent adverse reactions that may impact patient tolerability as discussed in Section 7.7 of the IRT. (b) (4)
7 DRUG INTERACTIONS	
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy and 8.2 Lactation subsections were developed consistent with the PLLR Review Tool. Descriptions of nonclinical data were updated to be consistent with PLLR guidelines. (b) (4) (b) (4) 8.4 Pediatric Use subsection included the pediatric use statement for pediatric patients aged 12 years and older, which is supported by 41 pediatric patients in the ASPEN trial and additional PK. 8.5 Geriatric Use subsection included the statement in which there were sufficient information to detect differences in safety and/or effectiveness between geriatric patients 65 years of age and older and younger adults, and there were no observed differences.
9 DRUG ABUSE AND DEPENDENCE	Not applicable
10 OVERDOSAGE	This section was modified to consider contacting Poison Help line (1-800-222-1222) or medical toxicologist for management recommendations.
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action: This section was edited to remove (b) (4) and edited for clarity. 12.2 Pharmacodynamics subsection: NSP activity in patients with NCFB was described. The Cardiac Electrophysiology information was revised to reflect the recommendation from the IRT review dated 1/24/25. 12.3 Pharmacokinetics subsection was revised to provide general PK information following administration of 10 mg or 25 mg brensocatib. Section 12.3 was developed consistent with clinical pharmacology labeling practices.
13 NONCLINICAL TOXICOLOGY	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility subsection was revised to be consistent with Division labeling practices. (b) (4) (b) (4)
14 CLINICAL STUDIES	This section was (b) (4) • Organize and present all clinical trial data from ASPEN first followed by data from WILLOW, including the order of presentation in Table 2. • Consolidate all primary and key secondary efficacy data from ASPEN into a single table (Table 3). (b) (4)

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	(b) (4) • (b) (4) cumulative mean number of pulmonary exacerbations
17 PATIENT COUNSELING INFORMATION	Added Dermatologic Adverse Reactions for healthcare providers to counsel patients regarding the risk for adverse skin events with Brinsupri use and to monitor skin for development of new skin rash or lesion. Added Gingival and Periodontal Adverse Reactions for healthcare providers to counsel patients regarding the risk for gingival and periodontal events with Brinsupri use, to advise patients to have regulator dental check-ups and perform routine dental hygiene while on Brinsupri. Live Attenuated Vaccines is included in Section 17 for healthcare providers to counsel patients regarding the use of Brinsupri prior to potential vaccination.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Sections 3, 11, and 16 were developed consistent with the considerations for product quality information in PI. Section 16: Formatted *How Supplied* information of brensocatib in a table (Table 4) to improve readability.

Source: Clinical Reviewer and Associate Director for Labeling.
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): ASPEN, Trial INS1007-301 (Study 301); DDD, Division of Dermatology and Dental Products; IRT, Integrated Review Template; LFT, liver function test; mg, milligram; NSP, neutrophil serine protease; PI, Prescribing Information; PK, pharmacokinetic; PLLR, Pregnancy and Lactation Labeling Rule; QOL-B, Quality of Life-Bronchiectasis; WILLOW, Trial INS1007-201 (Study 201)

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Package Insert
- Carton labeling
- Container labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirements and commitments are being issued at the time of regulatory action.

- PMR-1 Conduct a 52-week randomized, double-blind, placebo-controlled, parallel-group study in children 6 to 11 years of age (inclusive) with NCFB to assess efficacy, safety, and pharmacokinetic responses to brensocatib.
  - Final Protocol Submission: April 2027
  - Study Completion Date: December 2032
  - Final Report Submission Date: June 2033

25. Financial Disclosure

Table 116. Covered Clinical Trials: INS1007-201 and INS1007-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Trial INS1007-201: 467 investigators. Trial INS1007-301: 2,174 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): No investigators for Trials INS1007-201 and INS1007-301were Sponsor employees.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 21 investigators total with 11 investigators participating in both studies, 9 investigators in INS1007-301 only and 1 investigatory in INS1007-201 only.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 21 investigators Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: None Sponsor of covered study: Insmed Incorporated (Insmed)		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) Box 3 on Form FDA 3454 is not applicable as Insmed is both the Sponsor and the Applicant. No studies subject to providing financial disclosure information in the application were conducted by another firm or party.

Abbreviation: FDA, Food and Drug Administration

26. References

Guidances

FDA draft guidance for industry, food and drug administration staff, and other stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023)

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023a)

Guidelines

ICH harmonised guideline *Q3D(R2) Guideline for Elemental Impurities* (April 2022)

ICH scientific guideline *Q3C(R9) Guideline on Impurities: Guideline for Residual Solvents* (April 2024)

FDA guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators* (February 2013a)

ICH scientific guideline *Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* (February 2013b)

ICH scientific guideline *Q3B(R2) Impurities in New Drug Products* (June 2006)

ICH guidance for industry *Q3A Impurities in New Drug Substances* (June 2008)

ICH harmonised guideline *E6(R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice* (November 2016)

ICH harmonised tripartite guideline *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (October 1999)

ICH scientific guideline *M7(R2) Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (September 2023b)

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UniProt, 2025, P53634 · CATC_HUMAN UniProt Consortium.

27. Review Team

Table 117. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Thomas Yung/Ji LaRose (CPMS)
Nonclinical reviewer	Jahnabi Roy
Nonclinical team leader	Jessica Bonzo/Andrew Goodwin (tertiary)
OCP reviewer(s)	Lei He, Junshan Qiu, Manuela Grimstein
OCP team leader(s)	Amer Al-Khouja/Yunzhao Ren (tertiary), Jingyu (Jerry) Yu, Yuching Yang
Clinical reviewer	Elise Ferre
Clinical team leader	Elisabeth Boulos
Biometrics reviewer	Emily Shives
Biometrics team leader	Yongman Kim/Weiya Zhang (tertiary)
Cross-discipline team leader	Elisabeth Boulos
Division director (clinical)	Banu Karimi-Shah
Office director (or designated signatory authority)	Kathleen Donohue

Abbreviations: CPMS, Clinical Pharmacology Modeling and Simulation; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 118. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ/ATL	Craig Bertha/Julia Pinto (TL)
OPQ/Drug Substance	Sam Bain/Larry Perez (TL)
OPQ/DP	Austin Yu/Craig Bertha (TL)
OPQ/Biopharmaceutics	Kamrun Nahar/Tapash Ghosh (TL)
OPQ/OPMA	Du Ju/Shu-Wei Yang (TL)
RBPM	Emma Gimose
Clinical Data Scientist (CDS)	Leora Willner/Qunshu Zhang (TL)
OSI	Suyoung (Tina) Chang/Phillip Kronstein (TL)
OSE/DMEPA	Lissa Owens/Damon Birkemeier (TL)
OSE/DPV	Scott Janiczak
OSE/DEPI	Margie Goulding/Monique Falconer (TL)
OSE SRPM	Cristina Attinello/Ameet Joshi (TL)
OPDP	Quynh-Nhu Capasso/Meeta Patel
PLT	Tisa Ellis/Marcia Williams (TL)
DRM	Stephanie Olumba/Carolyn Tieu (TL)
DCOA	Ji Li/Onyeka Illoh (TL)
PFSS	Shuangshuang (Reni) Xu/Monica Morell (TL)
DDD	Felisa Lewis/Jill Lindstrom
ADL	Jessica Lee

Abbreviations: ADL, Associate Director for Labeling; ATL, Application Technical Lead; DCOA, Division of Clinical Outcome Assessment; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DDD, Division of Dermatology and Dental Products; DP, Drug Product; DPV, Division of Pharmacovigilance; DRISK, Division of Risk Management; DRM, Division of Risk Management; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations, PFSS, Patient Focused Statistical Scientist; PLT, Patient Labeling Team; RBPM, Regulatory Business Process Manager; SRPM, Safety Regulatory Project Manager; TL, team leader

27.1. Reviewer Signatures

Table 27-119 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Thomas Yung ORO DROII	Sections: 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Thomas Yung			**Digitally signed by Thomas Yung** **Date: 8/6/2025 5:38 PM EDT** **GUID: 202586213835**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yongman Kim OB DBIII	Sections: 6.2, 6.3, 15.1.4, 15.2.4, 16.1, 16.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yongman Kim			**Digitally signed by Yongman Kim** **Date: 8/6/2025 6:06 PM EDT** **GUID: 20258622626**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Andrew Goodwin OII DPTII	Sections: 5,7,8.4,13,23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Andrew Goodwin

Digitally signed by Andrew Goodwin

Date: 8/6/2025 6:35 PM EDT
GUID: 202586223513

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Ji Hyun Larose ORO DROII	Sections: 112	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Ji Hyun Larose

Digitally signed by Ji Hyun Larose

Date: 8/6/2025 6:52 PM EDT
GUID: 202586225244

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Jingyu Yu OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jingyu Yu			**Digitally signed by Jingyu Yu** **Date: 8/6/2025 7:39 PM EDT** **GUID: 202586233912**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Amer Al-Khouja OCP DIIP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amer Al-Khouja			**Digitally signed by Amer Al-Khouja** **Date: 8/7/2025 6:35 AM EDT** **GUID: 202587103556**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Jessica Bonzo OII DPTII	Sections: 5.1, 7.1, 8.3, 8.4, 13, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jessica Bonzo			**Digitally signed by Jessica Bonzo** **Date: 8/7/2025 6:41 AM EDT** **GUID: 20258710413**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Jahnabi Roy OII DPTII	Sections: 5.1, 7.1, 8.3, 8.4, 13, and 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jahnabi Roy			**Digitally signed by Jahnabi Roy** **Date: 8/7/2025 7:22 AM EDT** **GUID: 202587112241**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Secondary Reviewer	Monica Morell OB DBIII	Sections: 6.3.3, 16.1.4	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Monica Morell			**Digitally signed by Monica Morell** **Date: 8/7/2025 7:48 AM EDT** **GUID: 202587114818**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Data Scientist Discipline Secondary Reviewer	Qunshu Zhang	Sections: 7.6, 17	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Qunshu Zhang			**Digitally signed by Qunshu Zhang** **Date: 8/7/2025 7:56 AM EDT** **GUID: 20258711564**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Data Scientist Discipline Primary Reviewer	Leora Willner OND	Sections: 7.6, 17	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Leora Willner

Digitally signed by Leora Willner

Date: 8/7/2025 8:01 AM EDT
GUID: 20258712122

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Junshan Qiu OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Junshan Qiu

Digitally signed by Junshan Qiu

Date: 8/7/2025 8:30 AM EDT
GUID: 202587123035

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Primary Reviewer	Shuangshuang Xu OB DBIII	Sections: 6.3.3, 16.1.4	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shuangshuang Xu			**Digitally signed by Shuangshuang Xu** **Date: 8/7/2025 8:34 AM EDT** **GUID: 202587123446**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Jessica Lee OII DPACC	Sections: Section 23	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Jessica Lee			**Digitally signed by Jessica Lee** **Date: 8/7/2025 7:00 AM EDT** **GUID: 20258711055**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Emily Shives OB DBIII	Sections: 6.2, 6.3, 15.1.4, 15.2.4, 16.1, 16.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Emily Shives			**Digitally signed by Emily Shives** **Date: 8/7/2025 8:52 AM EDT** **GUID: 20258712523**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Elisabeth Boulos OII DPACC	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 12, 15, 16, 17, 23, 24	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elisabeth Boulos			**Digitally signed by Elisabeth Boulos** **Date: 8/7/2025 8:54 AM EDT** **GUID: 20258712546**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Yuching Yang OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang			**Digitally signed by Yuching Yang** **Date: 8/7/2025 8:54 AM EDT** **GUID: 20258712549**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Lei He OCP DIIP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lei He			**Digitally signed by Lei He** **Date: 8/7/2025 8:59 AM EDT** **GUID: 202587125950**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Ji Li ODES DCOA	Sections: 6.3.3, 16.1.4.2, 16.1.4.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ji Li			**Digitally signed by Ji Li** **Date: 8/7/2025 9:55 AM EDT** **GUID: 202587135558**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Karen Higgins OB DBIII	Sections: 6.2, 6.3, 15.1.4, 15.2.4, 16.1, 16.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Karen Higgins			**Digitally signed by Karen Higgins** **Sign on behalf of signing for Weiya Zhang** **Date: 8/7/2025 9:58 AM EDT** **GUID: 202587135820**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Onyekachukwu Illoh ODES DCOA	Sections: 6.3.3, 16.1.4.2, 16.1.4.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Onyekachukwu Illoh			**Digitally signed by Onyekachukwu Illoh** **Date: 8/7/2025 10:00 AM EDT** **GUID: 20258714021**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Elisabeth Boulos OII DPACC	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 12, 15, 16, 17, 22, 23, 24, 25	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elisabeth Boulos			**Digitally signed by Elisabeth Boulos** **Date: 8/7/2025 10:24 AM EDT** **GUID: 202587142440**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Elisabeth Boulos OII DPACC	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elisabeth Boulos			**Digitally signed by Elisabeth Boulos** **Date: 8/7/2025 10:25 AM EDT** **GUID: 202587142542**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Chandrahas Sahajwalla OCP DIIP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chandrahas Sahajwalla			**Digitally signed by Chandrahas Sahajwalla** **Sign on behalf of Signing off on behalf of Yunzhao Ren** **Date: 8/7/2025 11:37 AM EDT** **GUID: 202587153758**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Yuching Yang OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang			**Digitally signed by Yuching Yang** **Sign on behalf of Proxy for Manuela Grimstein** **Date: 8/7/2025 3:02 PM EDT** **GUID: 20258719231**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Tertiary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Craig Bertha			**Digitally signed by Craig Bertha** **Date: 8/11/2025 6:04 AM EDT** **GUID: 202581110411**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Craig Bertha

Digitally signed by Craig Bertha

Date: 8/11/2025 6:04 AM EDT
GUID: 202581110435

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Craig Bertha

Digitally signed by Craig Bertha

Date: 8/11/2025 6:04 AM EDT
GUID: 202581110459

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/

ELISABETH S BOULOS
08/11/2025 09:19:22 AM

BANU A KARIMI SHAH
08/11/2025 09:26:08 AM

KATHLEEN M DONOHUE
08/11/2025 12:26:10 PM