EU Risk Management Plan
for
BRINSUPRI

(Brensocatib)

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List of Abbreviations

Abbreviation	Definition
ABPA	Allergic bronchopulmonary aspergillosis
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CF	Cystic fibrosis
CL/F	Apparent clearance
C_{max}	Maximum concentration
CMQ	Customised MedDRA Query
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRSsNP	Chronic rhinosinusitis without nasal polyps
DPP1	Dipeptidyl peptidase 1
dP/dtmax	Maximal rate of rise of the left ventricular pressure
EAIR	Exposure adjusted incidence rate
EAP	Expanded Access Programme
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMBARC	European Bronchiectasis Registry
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HBV	Hepatitis B virus
hERG	Human Ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HR	Heart rate
IC_{50}	Half-maximal inhibitory concentration
LLT	Lowest Level Term
LVEDP	Left ventricular end diastolic pressure
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose

Abbreviation	Definition
N/A	Not applicable
NCFBE	Non-cystic fibrosis bronchiectasis
NOEL	No-Observed-Effect Level
NSP	Neutrophil serine protease
NTM	Nontuberculous mycobacteria
PASS	Post-authorisation safety study
PK	Pharmacokinetic
PLD	Phospholipidosis
PLS	Papillon-Lefèvre Syndrome
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q	Quarter
QA interval	Quantal analysis interval
QD	Once a day
QPPV	Qualified Person for Pharmacovigilance
QTcF	QT corrected for heart rate by Fridericia's cube root formula
QWBA	Quantitative whole-body autoradiography
RMP	Risk Management Plan
SAD	Single ascending dose
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TBD	To be determined
UK	United Kingdom
ULN	Upper limit of normal
US	United States
Vd/F	Volume of distribution

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Brensocatib
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Insmed Netherlands B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	BRINSUPRI 25 mg film-coated tablets
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Brensocatib belongs to a class of organic compounds known as beta amino acids and derivatives. Chemical class: Carboxylic acid and derivatives Chemical formula: $C_{23}H_{24}N_4O_4$
	Summary of mode of action: Brensocatib is an oral, selective, competitive, and reversible inhibitor of dipeptidyl peptidase 1 (DPP1). DPP1 activates pro inflammatory neutrophil serine proteases (NSPs) during neutrophil maturation in the bone marrow. Activated NSPs are implicated in the pathogenesis of many neutrophil-mediated inflammatory diseases, including bronchiectasis. Brensocatib reduces the activity of NSPs including neutrophil elastase, cathepsin G and proteinase 3.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Brensocatib Product Information (Module 1.3)
Indication(s) in the EEA	Current (if applicable): BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis in patients 12 years of age and older with two or more exacerbations in the prior 12 months.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): The recommended dosage of BRINSUPRI is 25 mg orally once daily with or without food.
	Proposed (if applicable): Not applicable

Pharmaceutical form(s) and strengths	Current (if applicable): BRINSUPRI 25 mg film-coated tablets Each film-coated tablet contains brensocatib monohydrate equivalent to 25 mg of brensocatib.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFBE) in patients 12 years of age and older with two or more exacerbations in the prior 12 months.

NCFBE is a chronic inflammatory lung disease characterised by localised and irreversible enlargement of the bronchi and bronchioles that may lead to obstructed breathing caused by abnormal mucus production. The severe pulmonary dysfunction and airway wall thickening associated with bronchiectasis is due to chronic inflammation and/or infection.

Incidence and Prevalence:

The epidemiology of bronchiectasis is influenced by regional differences with respect to aetiology and microbiology (Chandrasekaran 2018).

In 2013 the prevalence of bronchiectasis in United Kingdom (UK) women was 566/100,000 and in men 486/100,000 (Quint 2016). The prevalence and incidence of bronchiectasis in primary care in Italy in 2015 was 163 per 100,000 population and 16.3 per 100,000 person-years, respectively. Prevalence and incidence increased with age and overall rates were highest in men over 75 years old. Prevalence and incidence computed after the exclusion of patients with a diagnosis of either asthma or chronic obstructive pulmonary disease (COPD) was 130 per 100,000 and 11.1 cases per 100,000 person-years, respectively (Aliberti 2020). In the Catalonia Region (Spain) prevalence of NCFBE in 2012 was reported as 36.2 cases per 10,000 inhabitants, with an incidence of 4.81 cases per 10,000 inhabitants, both increased with age and were highest in men over 65 years of age, 56% had at least one exacerbation and 12.5% had been admitted to hospital during the year of the study (Monteagudo 2016). In Germany, an NCFBE incidence of 21.23 per 100,000 inhabitants was reported in 2013 (Diel 2019). The average annual age-adjusted rate of hospitalisations for bronchiectasis as any diagnosis in Germany over the period 2005-2011 was 9.4 per 100,000 population with a peak at 39.4 per 100,000 population among men aged 75-84 years (Ringshausen 2013).

The 8-year period prevalence of bronchiectasis in patients ≥65 years was 1,106 cases per 100,000 people utilising data from the United States (US) Medicare outpatient claims database from 2000 to 2007 with an annual prevalence increase of 8.7% (Seitz 2012). In a retrospective cohort study (2009–2013) the overall prevalence of NCFBE was estimated to be 139 cases per 100,000 US adults aged ≥18 years and 562 cases per 100,000 in those aged ≥65 years. The overall annual incidence of NCFBE was estimated to be 29 cases per 100,000 US adults aged ≥18 years (Weycker 2017). Data from 12 US states over the period 1993–2006 demonstrate an average annual age-adjusted hospitalisation rate of 16.5 hospitalisations per 100,000 population. Women and those aged over 60 years had the highest rate of hospitalisations (Seitz 2010).

A population-based study using data between 2013 and 2017 from the national medical insurance databases in China estimated the prevalence of bronchiectasis in adults ≥18 years of 75.48 (62.26, 88.69) per 100,000 patient-years in 2013 increasing to 174.45 (137.02, 211.88) per 100,000 patient-years in 2017 (Feng 2022). In a retrospective study, 129 of 1,409 (9.1%) adult patients who underwent chest CT scans in a South Korean centre during 2008 were diagnosed with bronchiectasis (Kwak 2010). New Zealand hospital admission rates for NCFBE are reported as 25.7 per 100,000 (Bibby 2015).

Demographics of the population in the proposed indication:

Bronchiectasis can affect all ages but its prevalence increases with age and it is more prevalent in females (Ringshausen 2013, Kwak 2010, Quint 2016). Weycker et al found that the annual incidence of NCFBE ranged from 2 per 100,000 persons aged 18 - 34 years to 154 per 100,000 persons aged ≥75 years. The incidence was also 1.1. to 1.5 times higher in women than in men at all ages (Weycker 2017).

Utilising data from the US Medicare outpatient claims database from 2000 to 2007, Seitz et al found the prevalence of bronchiectasis in patients ≥65 years was 2.5- and 3.9- times higher in Asians than whites and blacks (Seitz 2012).

Risk factors for bronchiectasis:

- Previous childhood viral respiratory infections (measles, influenza, whooping cough)
- Bacterial infections (Mycobacterium: Tuberculosis and atypical, Haemophilus influenzae, Pseudomonas aeruginosa, Staphylococcus aureus, Mycoplasma)
- Allergic bronchopulmonary aspergillosis (ABPA)/hypersensitivity pneumonitis
- Immunodeficiency (hypogammaglobulinemia)
- Human Immunodeficiency Virus (HIV)
- Genetic (cystic fibrosis (CF), Ciliary dyskinesia or immotile cilia syndrome, Alpha-1-antitrypsin deficiency)
- Aspiration or inhalation injury (gastroesophageal reflux disorder)
- Focal bronchial obstruction (foreign body, tumour, mucus plug)
- Pulmonary diseases (COPD, asthma, Idiopathic pulmonary fibrosis [traction bronchiectasis])
- Inflammatory/connective tissue diseases (rheumatoid arthritis, Sjögren's syndrome, and ulcerative colitis/Crohn's disease)

(Bird 2023, Bronchiectasis - Causes - NHS (www.nhs.uk))

Main existing treatment options:

There are currently no therapies specifically approved for treating NCFBE in the EU. Clinical management of patients with bronchiectasis includes mucoactive drugs, bronchodilators, and inhaled steroids, and in selected patients with high rates of exacerbations thought to be attributable to bacterial colonization, prophylactic antibiotics are utilised.

The evidence base for exacerbation prevention in bronchiectasis remains relatively poor. The first international guideline for bronchiectasis management was published by the European Respiratory Society in 2017 (Polverino 2017). Of the major therapy recommendations only one showed an effect on time to first exacerbation, namely pulmonary rehabilitation. Macrolides certainly reduce exacerbation frequency in a proportion of patients, but many clinicians are cautious about their use because of the risk of adverse events and concern about inducing macrolide resistance particularly, in the case of nontuberculous mycobacterial infection. Pooled analyses of inhaled antibiotic studies in bronchiectasis suggest that they reduce exacerbations by approximately 30%, but positive phase 3 trials have proved elusive (Polverino 2017; Chalmers 2018).

European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis were published more recently (Chang 2021).

Adult and paediatric guidelines recommend treatment of acute exacerbations with antibiotics for at least 14 days, prescribed according to expert opinion. Antibiotic selection is determined by known or suspected lower airway pathogens, local antibiotic availability and susceptibility profiles, age of patient, severity of the lung disease, comorbidities, antibiotic tolerance, and previous responses to treatment. Ideally, sputum should be sent for culture and, if a non-severe exacerbation, oral antibiotics active against the most common pathogens should be used. Those with severe episodes, not improving with oral agents, or featuring drug-resistant pathogens, such as Pseudomonas aeruginosa, might need intravenous antibiotics. Long-term use of antibiotics (>3 months) is recommended for those experiencing frequent exacerbations of more than three per year (Redding 2009; Chang 2015; Polverino 2017; Hill 2019; Chang 2021).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Patients with NCFBE suffer from a serious condition. In addition to symptoms of persistent cough, frequent exacerbations have a detrimental effect on quality of life. In 2013, Quint et al found the age-adjusted mortality rate of bronchiectasis in the UK was more than twice that for the general population (1437.7 per 100,000 vs 635.9 per 100,000 in women; 1914.6/100,000 vs 895.2/100,000 in men) (Quint 2016). The mortality rate of outpatient NCFBE patients followed in a UK referral centre from 1994 to 2007 was 29.7%. In comparison, the expected death rate in the general population at an age corresponding to the mean age of the study using life expectancy data from the Office of National Statistics for a similar 13-year period was 14.7% for males and 8.9% for females (Loebinger 2009). In Belgium the overall mortality in NCFBE patients who had a median follow-up of 5.18 years between 2006 and 2012 was 20.4%. Patients with NCFBE and associated COPD had a mortality of 55% in that period. Multivariate analysis showed significant higher mortality with increasing age, with increasing number of lobes affected and when patients had COPD associated NCFBE (Goeminne 2014).

A US longitudinal study described 30% mortality at 1-year follow-up post bronchiectasis exacerbation (Finklea 2010).

Important co-morbidities:

Important co-morbidities include asthma, COPD, HIV, rheumatoid arthritis, other connective tissue diseases, inflammatory bowel disease, bone marrow transplant, hypogammaglobulinemia, and ABPA (Quint 2016).

Part II: Module SII - Non-clinical part of the safety specification

Toxicity

Key safety findings from non-clinical toxicity studies and relevance to human usage are summarised below.

Repeat-dose toxicity studies

In 1-month studies, with doses in rats up to 100 mg/kg/day (Study No. 527409) and dogs up to 75 mg/kg/day (Study No. 527414) microscopic findings in the skeletal muscle, liver, thymus, and bone marrow, were noted at the highest dose levels; however, these findings were not observed in the 6-month studies (Module 2.6.6 Sections 3.1.2 and 3.2.2).

In a 6-month rat study (Study No. 528313), oral administration of brensocatib at 3, 9 or 50 mg/kg/day resulted in microscopic changes in the kidney (basophilic tubules in the outer medulla) and the lung (perivascular neutrophil infiltration, and vacuolated macrophage accumulation consistent with phospholipids) at 50 mg/kg/day (AUC 150 times the maximum recommended human dose [MRHD]). The findings in the kidney and lung at 50 mg/kg/day were completely reversible following a 3-month dose-free period. The no observed adverse effect level (NOAEL) was considered to be 9 mg/kg/day (AUC 20 times the MRHD) (Module 2.6.6 Section 3.1.3, Module 2.6.6 Section 9.2 Table 20).

In a 9-month dog study (Study No. 505523), oral administration of brensocatib at 1, 2, 4, or 8 mg/kg/day resulted in no adverse findings at any dose (AUC 5 times the MRHD) (Module 2.6.6. Section 3.2.4, Module 2.6.6 Section 9.2 Table 20). In a preceding 6-month dog study (Study No. 528329) at 2, 8 and 50 mg/kg/day, administration of brensocatib at 50 mg/kg/day caused periodontal disease resulting in early termination of the group. At ≥8 mg/kg/day (AUC 7 times the MRHD), dose-dependent microscopic findings were noted in the testis (seminiferous tubule degeneration and atrophy) and epididymis (decreased number of spermatozoa and cellular debris), and in the lung (accumulations of vacuolated macrophages consistent with phospholipids). AUC 150 times the maximum recommended human dose [MRHD] and in the lymphoid tissues (axillary, mandibular and mesenteric lymph nodes, gut associated lymphoid tissue and spleen) as indicated by the accumulations of vacuolated macrophages (Module 2.6.6 Section 3.2.3, Module 2.6.6 Section 9.2 Table 20).

Relevance to human usage:

The morphological changes in the lung and lymphoid tissues are consistent with phospholipidosis, which is a well-described phenomenon associated with cationic amphiphilic drugs similar to brensocatib in the literature. The periodontal disease is believed to be an on-target effect but not clinically relevant. All brensocatib-related toxicity findings were dose-dependent, reversible, and occurred at exposures greater than that at the maximum recommended clinical dose. Furthermore, to the extent possible, potential target organ toxicity identified in animals was closely monitored in clinical studies with brensocatib. To date, no associated safety concerns have been identified in humans.

Genotoxicity

There was no sign of genotoxicity in an in vitro Ames reverse mutation assay (Study No. 8304016), an in vitro mouse lymphoma mutation assay (Study No. 8304015), and an in vivo micronucleus study in rats (Study No. 830417) with brensocatib (Module 2.6.6 Sections 4.1.1, 4.1.2, 4.2.1).

Relevance to human usage:

Based on the above studies brensocatib does not pose a genotoxic risk to humans.

Carcinogenicity

In a 2-year carcinogenicity study in rats (Study No. 8002910), oral administration of brensocatib at doses of 3, 10, or 30 mg/kg/day was not carcinogenic at up to the highest dose (AUC up to 56 times the MRHD) (Module 2.6.6 Section 5.2.1, Module 2.6.6 Section 9.2 Table 20).

In a 6-month carcinogenicity study in transgenic rasH2 mice (Study No. 20354490), oral administration of brensocatib at doses of 5, 15, or 50 mg/kg/day was not carcinogenic at up to the highest dose (AUC 52 times the MRHD) (Module 2.6.6 Section 5.1.2, Module 2.6.6 Section 9.2 Table 20).

Relevance to human usage:

Brensocatib is not genotoxic and does not pose a carcinogenic risk to humans.

Reproductive and developmental toxicity

In a rat fertility and embryo-foetal development study (Study No. 497825), slight maternal toxicity as indicated by changes in body weight gain and food consumption was noted at 20 or 100 mg/kg/day (AUC ≥42 times the MRHD). The recoverable minor malformations of bent scapula and wavy ribs were only noted at 100 mg/kg/day. An increased incidence of skeletal variations (malpositioned pelvic girdle and vestigial supernumerary full and/or short ribs in both cervical and thoracolumbar regions) and differences in ossification were noted at 20 or 100 mg/kg/day. The NOAEL for maternal or development toxicity was considered to be 3 mg/kg/day (AUC 3 times the MRHD) (Module 2.6.6 Section 6.2.2, Module 2.6.6 Section 9.2 Table 20).

In a rabbit embryo-foetal development study (Study No. 497830), oral administration of brensocatib at 5, 15, or 50 mg/kg/day from Gestation Days 7 to 19 had no effect on embryofoetal survival and no notable effects on foetal development up to the top dose of 50 mg/kg/day (AUC 20 times the MHRD). Slight maternal toxicity as indicated by reductions in body weight gain and food consumption was noted at 50 mg/kg/day (Module 2.6.6 Section 6.2.5, Module 2.6.6 Section 9.2 Table 20).

In a pre- and post-natal development study (Study No. 00335001), oral administration of brensocatib to pregnant rats at doses of 3, 9, or 20 mg/kg/day from Gestation Day 6 through Lactation Day 20 resulted in no adverse findings at any dose for F0 parental systemic toxicity, F1 neonatal, developmental, systemic, and reproductive toxicity, and F2 embryonic survival (AUC 17 times the MRHD) (Module 2.6.6 Section 6.3.1, Module 2.6.6 Section 9.2 Table 20). Toxicokinetic analysis of plasma samples taken 3 hours postdose on Lactation Day 4 indicated that brensocatib concentrations increased with dose in both dams and pups. These results suggest that brensocatib is excreted into milk in lactating rats (Module 2.6.4 Section 3.3.2.7 and 6.3).

Relevance to human usage:

Although animal developmental studies did not reveal major anomalies, recoverable minor skeletal malformations of bent scapula and wavy ribs were observed in rats with foetal exposure to brensocatib. Considering brensocatib is the first-in-class medicinal product, and there is a lack of clinical data in pregnant women, embryo-foetal toxicity is considered as a safety concern (important potential risk) in the RMP. Brensocatib therapy is not recommended during pregnancy and in women of childbearing potential not using contraception.

Available data in animals suggest excretion of brensocatib in breastmilk. There is no information regarding the presence of brensocatib and/or its metabolite(s) in human milk. As a risk to the newborns/infants cannot be excluded, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from brensocatib therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Use of brensocatib during breast-feeding is included as a safety concern (missing information) in the RMP.

Safety Pharmacology

Key safety findings from safety pharmacology studies and relevance to human usage are summarised below.

Central Nervous system

Brensocatib was given by oral gavage to rats at doses of 0.5, 10, or 200 mg/kg and was without effect on autonomic, neuromuscular, sensorimotor, or behavioural parameters as assessed in the modified Irwin Screen (Study No. 612483). The No-Observed-Effect Level (NOEL) was considered to be 200 mg/kg (Module 2.6.2 Section 4.1).

Relevance to human usage:

The animal study did not indicate a safety concern. In addition, the clinical studies have not indicated a safety concern relating to the nervous system.

Cardiovascular

Brensocatib blocked the human Ether-à-go-go-Related Gene (hERG)-encoded potassium channel with an IC_{50} of 13.9 µM (Study No. 795027). The safety margin to the free exposure (C_{max}) at steady state in humans at a QD dose of 25 mg (C_{max} = 259 ng/mL; Study ICPD_00694-1) is 176-fold (Module 2.6.2 Section 4.2.1).

Brensocatib, given to anaesthetised guinea pigs at successive IV infusion doses of 0.5 and 9.6 mg/kg had no statistically significant effect on ventricular repolarization or intracardiac conduction (Study No. 0339SG). There were also no effects on mean arterial blood pressure or heart rate (HR) during sinus rhythm when compared to the vehicle group data (Module 2.6.2 Section 4.2.2).

Brensocatib was given by oral gavage to telemetered Beagle dogs at doses of 5, 50, and 1000 mg/kg (Study No. VKS0880). There were no effects on cardiovascular parameters at 5mg/kg and only a small increase in the QA interval at 50 mg/kg. At 1000 mg/kg, there was an increase in the heart rate accompanied by a transient decrease in the PR interval and an increase in the group mean diastolic and mean blood pressure, decreases in the maximal rate of rise of the left ventricular pressure (dP/dtmax) and the left ventricular end diastolic pressure (LVEDP) and an increase in the QA interval. At 1000 mg/kg, a small increase in the QT interval corrected for heart rate (6%) was also observed, but there were no effects on QRS, waveform morphology, or body temperature. Based on the results of this study with a No-Observed-Effect Level (NOEL) of 50 mg/kg and a clinical dose of 25 mg, the safety margin derived from the maximum observed concentration (C_{max}) in plasma is 43 (for free brensocatib) and 18 (for total brensocatib), indicating a low level of concern for cardiovascular effects (Module 2.6.2 Section 4.2.3).

Relevance to human usage:

The animal studies did not indicate a cardiovascular safety concern. In addition, a thorough QT study was also performed (INS1007-104) and was negative for cardiac effects in both the by timepoint and exposure effect analyses. No signal was observed for doses up to 120 mg or exposures ≤1550 ng/mL. In pooled Studies INS1007-301 and INS1007-201, mean

electrocardiogram measurements were generally stable during the studies, with little variation across treatment groups and no imbalance was observed for clinically meaningful changes from baseline. A QTcF interval >450 ms or a >30 ms change from baseline at any time during the study was reported for <10% of participants in both the brensocatib and placebo groups (Module 2.7.4 Section 5.2.1).

Respiratory System

The effects of brensocatib on respiratory rate, tidal volume, minute volume, inspiration and expiration times, and peak inspiratory and expiratory flows were assessed in male rats for up to 6 hours following a single oral dose of 0 (vehicle), 0.5, 10, or 200 mg/kg, using whole body plethysmography (Study No. 612499).

There were no statistically significant differences in any respiratory parameters that could be attributed to administration of brensocatib. The NOEL was considered to be 200 mg/kg (Module 2.6.2 Section 4.3).

Relevance to human usage:

The animal studies did not indicate a safety concern. In addition, there were no clinically relevant changes in vital signs across the treatment groups in any of the clinical studies (Module 2.5 Section 5.4.2).

Immunotoxicity

Potential immunotoxicity of brensocatib was assessed based on a weight-of-evidence approach (Study No. BRE-AB-IM-001 provided in Module 4.2.3.7.7) as summarised below:

Based on the pharmacological mode of action of brensocatib, the literature data that DPP1-/- mice maintained a preserved immune system and functionality, and the absence of general immune dysfunction in subjects with Papillon-Lefèvre Syndrome (PLS), inhibition of DPP1 with brensocatib is unlikely to have a generalised adverse effect on the immune system.

Database structure similarity search and visual inspections indicated that brensocatib does not resemble structures of common drugs that are known for immunomodulatory activity.

Based on the nature of immune-related findings in the lymphoid tissues (consistent with phospholipidosis [PLD]) noted in repeat dose general toxicity studies and the corresponding safety margins relative to the maximum clinical dose of 25 mg for NCFBE, no brensocatib-induced immunotoxicity is anticipated at the clinically relevant therapeutic dose and exposure.

In a rat quantitative whole-body autoradiography (QWBA) study, brensocatib-related radioactivity was not specifically retained at high concentrations in the immune organs and tissues. The presence of trace radioactivity in these tissues was not considered toxicologically significant, given that the only immune-related histological changes noted in repeat dose general toxicity studies in rats and dogs were the observation of PLD in the lymphoid tissues which occurred at doses that provided significant multiples of the clinically relevant exposure.

The major metabolite of brensocatib, thiocyanate, is an endogenous compound and not associated with immunotoxicity, and treatment with brensocatib clinically had no impact on the systemic exposure of thiocyanate.

Relevance to human usage:

No brensocatib-related increases in the incidence of adverse events related to immunotoxicity or autoimmunity have been observed the completed clinical programs. Review of adverse events from 6 studies (D6190C0001, D6190C0003, INS1007-101, INS1007-102, INS1007-103, and

INS1007-211) found no reported events with Preferred Terms (PTs) related to immunotoxicity or autoimmunity (Study No. BRE-AB-IM-001). In studies INS1007-201 and INS1007-301, treatment-emergent adverse events (TEAEs) from System Organ Class (SOC) Immune system disorders were reported in a similar rate across brensocatib and placebo groups. No TEAEs in this SOC showed a difference in incidence ≥1.0% between either brensocatib group and placebo; and all were assessed as not related (Module 5.3.5.1).

The comprehensive evaluations of the evidence available to date support that brensocatib has no potential for immunotoxicity at therapeutically relevant exposures.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for brensocatib comprises a total of 14 clinical studies (10 Phase 1 studies, 3 Phase 2 studies and 1 Phase 3 study). Approximately 1687 participants have been exposed to at least one dose of brensocatib within completed and ongoing clinical studies including 286 healthy subjects, 18 subjects with renal impairment, 18 subjects with hepatic impairment, 1,326 subjects with NCFBE, 24 subjects with CF, and 15 subjects with chronic rhinosinusitis without nasal polyps (CRSsNP) (Table 2).

Table 2: Cumulative Exposure to Brensocatib

Clinical Study	Population	Number of Subjects Exposed to Brensocatib
D6190C00001		
SAD Part 1a/ Part 1b[a]	Healthy Subjects	30
MAD Part	Healthy Subjects	24
D6190C00003	Healthy Subjects	15
INS1007-101	Healthy Subjects	69
INS1007-102	Healthy Subjects	10
	Subjects with renal impairment	18
INS1007-103	Healthy Subjects	7
INS1007-104	Healthy Subjects	44
INS1007-105	Healthy Subjects	9
	Subjects with hepatic impairment	18
INS1007-106	Healthy Subjects	32
INS1007-109	Healthy Subjects	22
INS1007-110	Healthy Subjects	24
INS1007-201	NCFBE	170
INS1007-211	Cystic Fibrosis	24
INS1007-221[b]	CRSsNP	15
INS1007-301	NCFBE	1,156
Total		**1,687**

Source: EU Module 2.7.4 Table 6

[a] Eight subjects from Part 1a were rolled to Part 1b, of which five received brensocatib and three received placebo. Those subjects are counted once in the total of subjects.

[b] Includes 15 of 23 subjects on blinded medication through 28 March 2024 since 2/3 subjects were exposed to brensocatib in this ongoing study (EU Module 2.7.4 Section 2.1).

CRSsNP = chronic rhinosinusitis without nasal polyps; MAD = multiple ascending dose; NCFBE = non-cystic fibrosis bronchiectasis; SAD = single ascending dose.

Table 3: Duration of Exposure by Dose in Studies INS1007-201 and INS1007-301 (Safety Analysis Set)

Characteristics	Brensocatib 10 mg QD n (%) (n=663)	Brensocatib 25 mg QD n (%) (n=663)	Placebo n (%) (n=648)	Pooled Brensocatib n (%) (n=1326)
Actual treatment duration (days)[a]				
Mean (SD)	313.0 (91.80)	310.7 (95.11)	309.4 (94.20)	311.8 (93.44)
Median	358.0	358.0	358.0	358.0
Min, Max	1,418	4,394	2,395	1,418
Actual treatment duration (patient-years)[b]	568.1	564.0	548.8	1132.1
Categories of actual treatment duration, n (%)				
<12 weeks	29 (4.4)	29 (4.4)	27 (4.2)	58 (4.4)
≥12 weeks to <24 weeks	50 (7.5)	58 (8.7)	51 (7.9)	108 (8.1)
≥24 weeks to <36 weeks	56 (8.4)	51 (7.7)	60 (9.3)	107 (8.1)
≥36 weeks to ≤52 weeks	385 (58.1)	361 (54.4)	361 (55.7)	746 (56.3)
>52 weeks	143 (21.6)	164 (24.7)	149 (23.0)	307 (23.2)
Cumulative duration of actual treatment, n (%)				
≥12 weeks	634 (95.6)	634 (95.6)	621 (95.8)	1268 (95.6)
≥24 weeks	584 (88.1)	576 (86.9)	570 (88.0)	1160 (87.5)
≥36 weeks	528 (79.6)	525 (79.2)	510 (78.7)	1053 (79.4)

Source: ISS Table 1.4-1 (EU Module 2.7.4 Table 8)

[a] Actual treatment duration (days) = exposure duration - number of missed doses due to any reasons

[b] Actual treatment duration (patient-years) = sum of actual treatment duration (years) contributed by all patients.

Percentages are calculated based on the total number of participants in the analysis set per treatment or overall as the denominator.

Max = maximum; Min = minimum; n = number of participants; QD = once a day; SD = standard deviation.

Table 4: Exposure to Brensocatib by Age Group and Sex in Studies INS1007-201 and INS1007-301 (Safety Analysis Set)

Characteristics	Brensocatib 10 mg QD n (%) (n=663)	Brensocatib 25 mg QD n (%) (n=663)	Placebo n (%) (N=648)	Pooled Brensocatib n (%) (N=1326)
Age (years)				
Mean (SD)	60.4 (15.62)	61.1 (15.43)	60.5 (15.08)	60.7 (15.52)
Median	64.0	65.0	64.0	65.0
Min, Max	12, 85	12, 85	12, 85	12, 85
Age group				
12 to <18 years	17 (2.6)	16 (2.4)	8 (1.2)	33 (2.5)
18 to <65 years	322 (48.6)	295 (44.5)	328 (50.6)	617 (46.5)
≥65 years	324 (48.9)	352 (53.1)	312 (48.1)	676 (51.0)
≥18 years	646 (97.4)	647 (97.6)	640 (98.8)	1293 (97.5)
<75 years	560 (84.5	565 (85.2)	542 (83.6)	1125 (84.8)
≥75 years	103 (15.5)	98 (14.8)	106 (16.4)	201 (15.2)
Sex				
Male	223 (33.6)	240 (36.2)	232 (35.8)	463 (34.9)
Female	440 (66.4)	423 (63.8)	416 (64.2)	863 (65.1)

Source: ISS Table 1.2.1-1 (EU Module 2.7.4 Table 9)
Max = maximum; Min = minimum; n = number of participants; QD = once daily; SD = standard deviation.

Table 5: Exposure to Brensocatib by Ethnicity and Race in Studies INS1007-201 and INS1007-301 (Safety Analysis Set)

Characteristics	Brensocatib 10 mg QD n (%) (n=663)	Brensocatib 25 mg QD n (%) (n=663)	Placebo n (%) (N=648)	Pooled Brensocatib n (%) (N=1326)
Ethnicity				
Not Hispanic or Latino	469 (70.7)	482 (72.7)	458 (70.7)	951 (71.7)
Hispanic or Latino	179 (27.0)	167 (25.2)	170 (26.2)	346 (26.1)
Not Reported	13 (2.0)	13 (2.0)	17 (2.6)	26 (2.0)
Unknown	2 (0.3)	1 (0.2)	3 (0.5)	3 (0.2)
Race				
American Indian or Alaska Native	8 (1.2)	6 (0.9)	9 (1.4)	14 (1.1)
Asian	68 (10.3)	69 (10.4)	77 (11.9)	137 (10.3)
Black or African American	2 (0.3)	7 (1.1)	5 (0.8)	9 (0.7)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.2)	2 (0.3)	3 (0.2)
White	506 (76.3)	510 (76.9)	474 (73.1)	1016 (76.6)
Other	15 (2.3)	14 (2.1)	11 (1.7)	29 (2.2)
Unknown	17 (2.6)	13 (2.0)	14 (2.2)	30 (2.3)
Not Reported	30 (4.5)	32 (4.8)	45 (6.9)	62 (4.7)
Multiple[a]	15 (2.3)	11 (1.7)	11 (1.7)	26 (2.0)

Source: ISS Table 1.2.1-1 (EU Module 2.7.4 Table 9)

[a] Multiple races can be selected by each participant.

n = number of participants; QD = once daily.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria for the Phase 3, randomised, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of brensocatib administered once daily for 52 Weeks in subjects with NCFBE (INS1007-301) are listed below together with the rationale for the exclusions:

Exclusion criteria:

- Subjects >85 years
- Subjects <12 years

Reason for exclusion

Subjects > 85 years were excluded to reduce potential confounders due to age-related comorbidities, quality of life, and predicted life expectancy. Older adults are at high risk for adverse drug reactions because of the pharmacokinetic and pharmacodynamic changes associated with aging (Herrera 2010).

Although adolescent subjects aged ≥12 to <18 years were included in Study INS1007-301 from participating countries and sites where local regulations, countries, and/or institutional policies allowed them to participate, in many countries it is standard practice to investigate new drugs in an adult population first. In the EU, a paediatric investigation plan has been agreed with a waiver for children from birth to 6 years and deferral for children from 6 years to <12 years (EMA-002905-PIP01-20-M01 06 SEP 2024).

Is it considered to be included as missing information? No

Rationale:

Children <12 years of age are not included in the proposed indication.

A safety analysis for the pooled NCFBE studies (INS1007-201 and INS1007-301) was performed for the following age groups 12 to <18, ≥18, 18 to <65, ≥65, <75, and ≥75 years. The overall incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups in all age subgroups. In the brensocatib 10 mg group, at least 1 TEAE was reported in 88.2%, 79.4%, 80.4%, 78.4%, 79.3%, and 81.6% of the participants in the 12 to <18, ≥18, 18 to <65, ≥65, <75, and ≥75 years of age subgroups, respectively. In the brensocatib 25 mg group, at least 1 TEAE was reported in 75.0%, 77.9%, 75.6%, 79.8%, 77.5%, and 79.6% of the participants in 12 to <18, ≥18, 18 to <65, ≥65, <75, and ≥75 years of age subgroups, respectively. The corresponding incidence for placebo was 87.5%, 79.4%, 78.7%, 80.1%, 78.8%, and 83.0% (Module 2.7.4 Section 6.1.2). Based on the safety profile to date in the elderly population, a different safety profile is not anticipated in patients >85 years of age.

Exclusion criteria:

Women of childbearing potential (i.e. not postmenopausal, not surgically sterile, or not using highly effective contraception from Day 1 to at least 90 days after the last dose). Male subjects with female partners of childbearing potential not using effective contraception from Day 1 to at least 90 days after the last dose.

Reason for exclusion:

The effects of brensocatib on human pregnancy are unknown.

Is it considered to be included as missing information? No

Rationale:

Embryo-foetal toxicity is an important potential risk of brensocatib in the RMP. The Summary of Product Characteristics (SmPC) includes a warning that treatment with brensocatib is not recommended during pregnancy and in women of childbearing potential not using contraception. Therefore, use of brensocatib in pregnant women is not recommended or expected. Any such use will be monitored using routine pharmacovigilance activities.

Exclusion criterion:

Severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min)

Reason for exclusion:

Pharmacokinetic (PK) studies had not been completed in these populations at the time of subject enrolment. Patients with severe renal impairment were also excluded to avoid potential confounders on study assessments due to baseline disease.

Is it considered to be included as missing information? No

Rationale:

A Phase 1, open-label, single-dose parallel-group study of brensocatib following a single oral administration at 25 mg in subjects with or without renal impairment has now been completed (INS1007-102). Compared to healthy controls, the systemic exposure was similar in the mild, slightly higher in the moderate, but slightly lower in the severe renally impaired participants, without apparent trend regarding the renal functions. Elimination half-life ($t_{½}$), apparent clearance (CL/F), and volume of distribution (Vd/F) were similar across all groups. Statistical evaluation using geometric mean ratios showed that brensocatib maximum observed concentration (C_{max}) was comparable across all groups. The area under the concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{∞}) was highly comparable between healthy and the mild groups while the AUCs were 27% higher for the moderate group and 28% lower for the severe group. Regression analyses showed no correlations between eGFR and PK parameters (eg, C_{max}, AUC, CL/F, and Vd/F) (P ≥0.239) (Module 2.7.2 Section 2.4.1).

Based on the PK results of Study INS1007-102, no dose adjustment is recommended in renally impaired patients and the safety profile of brensocatib is not expected to differ in patients with severe renal impairment. For this reason, severe renal impairment is not included as missing information in the list of safety concerns in the RMP.

Exclusion criterion:

Active liver disease or severe hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × upper limit of normal [ULN], total bilirubin >2 × ULN)

Reason for exclusion:

Pharmacokinetic (PK) studies had not been completed in these populations at the time of subject enrolment. Patients with severe hepatic impairment were also excluded to avoid potential confounders on study assessments due to baseline disease.

Is it considered to be included as missing information? No

Rationale:

A Phase 1, open-label study to evaluate the PK and safety of a single dose of brensocatib in subjects with normal hepatic function and subjects with hepatic impairment has been conducted (INS1007-105). The systemic exposure of brensocatib (total C_{max} and AUC) in mild and moderate participants was similar to that in healthy participants (≤20% difference), but slightly lower in participants with severe hepatic impairment (19% and 26% lower for AUC_{∞} and C_{max}). The elimination $t_{½}$, CL/F, V_d/F, and renal clearance (CL_R) were generally comparable between cohorts and no specific trend was observed, suggesting that brensocatib elimination was not meaningfully altered in the presence of hepatic impairment. No statistically significant relationships between brensocatib PK parameters and Child-Pugh scores were found (*P* values >0.05) (Module 2.7.2 Section 2.4.2).

Based on the PK results of Study INS1007-105, no dose adjustment is required in hepatically impaired patients and the safety profile of brensocatib is not expected to differ in patients with severe hepatic impairment. For this reason, severe hepatic impairment is not included as missing information in the list of safety concerns.

Exclusion criterion

Received any live attenuated vaccine within 4 weeks prior to Screening. If a live vaccine has been administered the subject should wait 4 weeks prior to Screening. During the study, subjects may not receive any live attenuated vaccine.

Reason for exclusion:

Concomitant use of brensocatib and live attenuated vaccines had not been evaluated. Patients with bronchiectasis may receive pneumococcal and annual seasonal influenza vaccines as well as other vaccines recommended by national authorities (Chang 2021, Hill 2019).

Is it considered to be included as missing information? No

Rationale:

The SmPC includes a warning that the concomitant use of live attenuated vaccines has not been evaluated and that these vaccines should be avoided in patients receiving brensocatib. Therefore, concomitant use of brensocatib with live attenuated vaccines is not recommended or expected. Any such use will be monitored using routine pharmacovigilance activities including signal detection.

Exclusion criteria

- CF
- A primary diagnosis of COPD or asthma as judged by the Investigator. Patients with comorbid COPD and/or asthma could be enrolled if bronchiectasis was their primary diagnosis.
- Required supplemental oxygen >12 hours per day
- Current smokers
- Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immunocompromised status, as judged by the Investigator.

- Any of the following infections: HIV, hepatitis B virus (HBV), hepatitis C virus, nontuberculous mycobacteria (NTM), ABPA, tuberculosis, or coronavirus disease 2019 (COVID-19).
- Oral or inhaled antibiotics as chronic treatment for NCFBE if they were started <3 months prior to the Screening Visit.
- Chronic treatment with oral steroids

Reason for exclusion:

The above criteria were in place to reduce potential confounders in efficacy assessments

Are they considered to be included as missing information? No

Rationale:

CF is not included in the proposed indication. Although some of the risk factors and conditions described above could lead to an exacerbation of bronchiectasis and confound efficacy assessments; these patients could benefit from treatment with brensocatib, and no additional safety concern is anticipated in these patients.

Exclusion criteria

- Diagnosed with periodontal disease and are either: (a) under active management by a dentist for this condition; or (b) are expected to have periodontal disease-related procedures within the study period
- Clinical diagnosis of Papillon-Lefèvre Syndrome (PLS)
- Severe concomitant illnesses that in the Investigator's judgment would adversely affect the subject's participation in the study.

Reason for exclusion:

The above criteria were in place to reduce potential confounders in safety assessments. Papillon-Lefèvre syndrome, a condition nearly devoid of DPP1 function, is a rare genetic disorder characterised by severe periodontal disease and palmoplantar hyperkeratosis (Korkmaz 2010, Sreeramulu 2015). Based on the mechanism of action of brensocatib, a DPP1 inhibitor, and known symptoms and susceptibilities in patients with PLS, severe infections, hyperkeratosis and periodontal/gingival events were included as adverse events of special interest (AESI) in the clinical trials. In addition, patients with PLS would not benefit from exposure to brensocatib.

Are they considered to be included as missing information? No

Rationale:

Brensocatib would not be efficacious in patients with PLS.

The clinical impact of brensocatib on periodontal disease and incidence of periodontal events was similar across treatment groups (placebo and brensocatib) in the clinical studies with no trend being observed. There was no evidence of an increased risk of severe infections overall or pneumonia events with brensocatib when compared to placebo. Hyperkeratosis is listed in the SmPC as a common adverse drug reaction (SVII.1.1.).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 6: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme (SVII.3.2.).
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	INS1007-105 Mild (Child-Pugh score 5 to 6): n=6 Moderate (Child-Pugh score 7 to 9: n=6 Severe (Child-Pugh score 10 to 15): n=6
• Patients with renal impairment	INS1007-102 Mild: n=6 Moderate: n=6 Severe: n=6
• Patients with cardiovascular impairment	INS1007-301 14.9% (251/1682) of the patients enrolled had cardiovascular disease (Chalmers 2024).
• Immunocompromised patients	INS1007-201 Selective IgG subclass deficiency: n=1 INS1007-301 Immunodeficiency: n=1 Common variable immunodeficiency: n=1 Hypogammaglobulinemia: n=1 Selective IgG subclass deficiency: n=1
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme

Type of special population	Exposure
Population with relevant different ethnic origin	No races or ethnic origin were excluded from the clinical studies. Participants exposed to brensocatib in pooled studies were predominantly white (76.6%) and not hispanic/latino (71.7%) (Table 5).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Brensocatib was approved by the US FDA for the treatment of NCFBE on 12 August 2025. No post-authorisation exposure data is available at the time of this report.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Brensocatib has been assessed for potential abuse liability (Study No. BRE-AB-IM-001 provided in Module 4.2.3.7.7). Brensocatib is deemed to have no potential for abuse, following comprehensive evaluations based on the pharmacological mechanism of action, structure similarity evaluation, an in vitro off-target screening assay, a dedicated Central Nervous System (CNS) safety pharmacology study, repeat dose general toxicity studies in rats and dogs which showed no clinical signs indicative of potential CNS-specific effects on abuse liability or drug dependence, a rat QWBA study suggesting negligible penetration across the blood brain barrier, and the fact that the major metabolite (thiocyanate) is an endogenous compound not associated with potential for abuse liability.

In completed clinical studies with brensocatib, there were no clinical data consistent with illicit use, abuse, or dependency with steady state exposure of brensocatib for up to 6 months in duration. The potential for drug abuse or dependence is not expected for brensocatib and there are currently no data to imply illicit use, abuse, or dependency with brensocatib (Module 2.6.6 Section 8.2).

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The following ADRs listed in the section 4.8 of the SmPC were not considered important risks for inclusion in the list of safety concerns in this RMP as they have minimal impact on patients (in relation to the severity of the indication treated):

- Upper respiratory tract infection
- Gastroenteritis
- Headache
- Gingival disorder
- Periodontal disease
- Hyperkeratosis
- Rash
- Dry skin
- Dermatitis
- Skin exfoliation
- Alopecia

Among these, additional information is provided for Hyperkeratosis, Gingival disorder, and Periodontal disease below.

Hyperkeratosis (Identified risk)

Papillon-Lefèvre syndrome, a condition nearly devoid of DPPI function, is a rare genetic disorder characterised by severe periodontal disease and palmoplantar hyperkeratosis (Korkmaz 2010, Sreeramulu 2015). Based on the mechanism of action of brensocatib, a DPPI inhibitor, hyperkeratosis was included as an AESI in the clinical trials.

A customised MedDRA query (CMQ) including all Preferred Terms (PTs) included in the High Level Term (HLT) hyperkeratosis and PTs of skin lesion, exfoliative rash, seborrheic keratosis, eczema, palmoplantar keratoderma (Lowest Level Term [LLT] hyperkeratosis palmaris and plantaris) and hyperkeratosis follicularis et parafollicularis was used to determine the incidence of hyperkeratosis in the safety analysis set of the pooled studies (Table 7).

All hyperkeratosis AESIs as reported by the Investigator were nonserious, mild or moderate in severity, most were deemed related to study treatment, and most resolved with no action taken with study treatment. In limited cases, however, actions such as treatment interruption/discontinuation, and/or study discontinuation were taken. Approximately half of participants with Investigator-assessed hyperkeratosis AESI were not treated. Of those who were

treated, the majority were treated with topical emollients or topical corticosteroids (Module 2.7.4 Section 3.1.5.2.1).

Hyperkeratosis is listed in the SmPC as a common adverse drug reaction. As evidenced by the clinical studies, the adverse reaction of hyperkeratosis had limited clinical impact (non-serious, mild or moderate severity) on the participants in relation to the severity of the indication treated. For this reason, hyperkeratosis is considered to be a non-important identified risk. Hyperkeratosis events will be followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting.

Table 7: Hyperkeratosis CMQ TEAEs (≥2 Participants) in Studies INS1007-301 and INS1007-201 (Safety Analysis Set)

System Organ Class Preferred Term	Brensocatib 10 mg QD (N = 663) n % m	Brensocatib 25 mg QD (N = 663) n % m	Pooled Brensocatib (N = 1326) n % m	Placebo (N = 648) n % m
Hyperkeratosis by CMQ				
Participants with at least one hyperkeratosis event, n (%) m EAIR	29 (4.4) 31 4.789	39 (5.9) 50 6.499	68 (5.1) 81 5.641	20 (3.1) 20 3.376
Risk difference brensocatib vs placebo (%)	1.2876	2.7959	N/A	N/A
Exact 95% confidence interval	-0.8043, 3.4479	0.4672, 5.1643	N/A	N/A
Skin and subcutaneous tissue disorders	26 (3.9) 28	34 (5.1) 41	60 (4.5) 69	19 (2.9) 19
Hyperkeratosis	8 (1.2) 8	16 (2.4) 18	24 (1.8) 26 (19 mild, 5 moderate)	4 (0.6) 4
Eczema	11 (1.7) 13	11 (1.7) 11	22 (1.7) 24 (21 mild, 1 moderate)	8 (1.2) 8
Skin lesion	4 (0.6) 4	9 (1.4) 11	13 (1.0) 15 (11 mild, 2 moderate)	6 (0.9) 6
Palmoplantar keratoderma	2 (0.3) 2	0	2 (0.2) 2 (1 mild, 1 moderate)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.5) 3	5 (0.8) 9	8 (0.6) 12	1 (0.2) 1
Seborrhoeic keratosis	3 (0.5) 3	5 (0.8) 9	8 (0.6) 12 (7 mild, 1 moderate)	1 (0.2) 1

Source: ISS Table 1.5.1-4, ISS Table 1.5.1-8b; ISS Table 1.5.1-5c (Module 2.7.4 Table 19 and Table 20)
CMQ = customised MedDRA Query; EAIR = exposure adjusted incidence rate (100 x [number of patients with events] / [total time at risk]); m = number of events; MedDRA = medical dictionary for regulatory affairs; n = number of participants experiencing events; N/A = not applicable; QD = once a day; TEAE = treatment emergent adverse event.

Periodontal/Gingival Events (Identified risk)

Papillon-Lefèvre syndrome, a condition nearly devoid of DPPI function, is a rare genetic disorder characterised by severe periodontal disease and palmoplantar hyperkeratosis (Korkmaz 2010, Sreeramulu 2015). Based on the mechanism of action of brensocatib, a DPPI inhibitor, periodontal/gingival events were included as an AESI in the clinical trials.

A CMQ including all PTs included in the standardised MedDRA Query (SMQ) gingival disorders plus PTs of periodontitis, oral pain, periodontal destruction, periodontal disease, and periodontal inflammation was used to determine the incidence of periodontitis in the safety analysis set of the pooled studies (Table 8). All periodontal/gingival events were nonserious and mild or moderate in severity except for 1 event in the placebo group in Study INS1007-301 that was severe. A total of 4 participants (1 in the brensocatib 10 mg group, 1 in the brensocatib 25 mg group, and 2 in the placebo group) had events that resulted in treatment discontinuation. Two additional participants in the brensocatib 10 mg group had events which resulted in both treatment discontinuation and discontinuation from the study. Two participants in the brensocatib 25 mg group had events for which drug was interrupted (Module 2.7.4 Section 3.1.5.2.2).

Gingival disorder and Periodontal disease are listed in the SmPC as common adverse drug reactions. However, the incidence of periodontal/gingival events (CMQ) was similar across treatment groups in the clinical studies with no trend being observed. The clinical impact was also minimal (non-serious, mild or moderate severity in brensocatib treatment group) in relation to the severity of the indication. For these reasons, periodontal/gingival events are considered non-important identified risks. Periodontal/gingival events will be followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting.

Table 8: Periodontal/Gingival CMQ TEAEs (≥ 2 Participants) in Studies INS1007-301 and INS1007-201 (Safety Analysis Set)

System Organ Class/Preferred Term	Brensocatib 10 mg QD (N = 663) n (%) m	Brensocatib 25 mg QD (N = 663) n (%) m	Pooled Brensocatib (N = 1326) n (%) m	Placebo (N = 648) n (%) m
Participants with at least one periodontal/gingival event, n (%) m EAIR	39 (5.9) 41 6.476	35 (5.3) 41 5.828	74 (5.6) 82 6.152	38 (5.9) 45 6.537
Risk difference brensocatib vs placebo (%)	0.0182	-0.5852	N/A	N/A
Exact 95% confidence interval	-2.6097, 2.6332	-3.1522, 1.9516	N/A	N/A
Gastrointestinal disorders	35 (5.3) 37	31 (4.7) 35	66 (5.0) 72	34 (5.2) 39
Gingival disorder	10 (1.5) 11	8 (1.2) 8	18 (1.4) 19 (14 mild, 4 moderate)	9 (1.4) 11
Gingival pain	8 (1.2) 8	9 (1.4) 12	17 (1.3) 20 (14 mild, 3 moderate)	13 (2.0) 15
Gingival bleeding	9 (1.4) 10	3 (0.5) 4	12 (0.9) 14 (12 mild)	4 (0.6) 4

System Organ Class/Preferred Term	Brensocatib 10 mg QD (N = 663) n (%) m	Brensocatib 25 mg QD (N = 663) n (%) m	Pooled Brensocatib (N = 1326) n (%) m	Placebo (N = 648) n (%) m
Periodontal disease	2 (0.3) 2	5 (0.8) 5	7 (0.5) 7 (6 mild, 1 moderate)	1 (0.2) 1
Oral pain	2 (0.3) 2	3 (0.5) 3	5 (0.4) 5 (5 mild)	0
Gingival discomfort	2 (0.3) 2	1 (0.2) 1	3 (0.2) 3 (3 mild)	3 (0.5) 3
Gingival recession	2 (0.3) 2	1 (0.2) 1	3 (0.2) 3 (3 mild)	1 (0.2) 1
Noninfective gingivitis	0	0	0	2 (0.3) 2
Infections and infestations	3 (0.5) 3	5 (0.8) 5	8 (0.6) 8	4 (0.6) 6
Gingivitis	1 (0.2) 1	3 (0.5) 3	4 (0.3) 4 (4 mild)	1 (0.2) 3
Periodontitis	2 (0.3) 2	2 (0.3) 2	4 (0.3) 4 (2 mild, 2 moderate)	3 (0.5) 3

Source: ISS Table 1.5.1-4, ISS Table 1.5.1.-7c and ISS Table 1.5.1-8b (Module 2.7.4 Table 19 and Table 21)
CMQ = customised MedDRA Query; EAIR = exposure adjusted incidence rate (100 x [number of patients with events] / [total time at risk]); m = number of events; MedDRA = medical dictionary for regulatory affairs; n = number of participants experiencing events; N/A = not applicable; QD = once daily; TEAE = treatment emergent adverse event.

<u>Risks defined as potential based on experience of patients with PLS which are not supported by clinical evidence</u>

- Severe infections/pneumonia

The experience of patients with PLS, a condition nearly devoid of DPPI function, was used to provide insights into potential risks of brensocatib, a DPPI inhibitor. A small proportion of patients with PLS are predisposed to recurrent non-serious infections, though true life threatening infections are uncommon (Korkmaz 2010, Sreeramulu 2015). Although PLS patients have a marked deficiency of DDP1, the patients do not show severe immunocompromise even though there is a lack of NSPs (Korkmaz 2018). Nonetheless, as a precaution, infections were defined as AESIs for diligent surveillance in the clinical trials.

Any TEAE assessed as severe and coding to the System Organ Class (SOC) infections and infestations was used to determine the incidence of severe infections in the safety analysis set of the pooled studies. In addition, all pneumonia TEAEs were analysed as a specific category.

The overall incidence of TEAEs in the Infections and infestations SOC was similar for all treatment groups (338 [51.0%], 335 [50.5%], and 337 [52.0%] for brensocatib 10 mg, brensocatib 25 mg, and placebo groups, respectively). Of these TEAEs, 43 (6.5%), 46 (6.9%), and 47 (7.3%) were serious and 20 (3.0%), 27 (4.1%), and 39 (6.0%) were severe for brensocatib 10 mg, brensocatib 25 mg, and placebo groups, respectively (ISS Table 1.5.1-2a, Table 1.5.1-2b, Table 1.5.1-4). Severe events within the SOC are presented in Table 9.

Table 9: Severe TEAEs in the Infections and Infestations SOC in Studies INS1007-301 and INS1007-201 (Safety Analysis Set)

PT	Brensocatib 10 mg QD (N = 663) n (%)	Brensocatib 25 mg QD (N = 663) n (%)	Placebo (N = 648) n (%)
Appendicitis	1 (0.2)	0	1 (0.2)
Aspergillus infection	1 (0.2)	0	0
Bronchitis	1 (0.2)	0	0
Chronic sinusitis	1 (0.2)	0	0
Coronavirus infection	0	0	1 (0.2)
COVID-19	2 (0.3)	6 (0.9)	3 (0.5)
COVID-19 pneumonia	0	0	1 (0.2)
Diverticulitis	0	1 (0.2)	1 (0.2)
Empyema	0	0	1 (0.2)
Gastoenteritis	0	1 (0.2)	0
Gastroenteritis cryptosporidial	1 (0.2)	0	0
Herpes zoster	0	0	1 (0.2)
Infective exacerbation of bronchiectasis	1 (0.2)	1 (0.2)	5 (0.8)
Influenza	2 (0.3)	0	2 (0.3)
Large intestine infection	1 (0.2)	0	0
Lung abscess	0	2 (0.3)	1 (0.2)
Mastitis	0	1 (0.2)	0
Pneumonia	6 (0.9)	10 (1.5)	17 (2.6)
Pneumonia aspiration	0	0	2 (0.3)
Pneumonia bacterial	0	1 (0.2)	1 (0.2)
Pneumonia necrotising	0	1 (0.2)	0
Pneumonia pneumococcal	0	0	1 (0.2)
Pneumonia pseudomonal	0	1 (0.2)	0
Postoperative wound infection	1 (0.2)	0	0
Pseudomonas infection	0	0	1 (0.2)
Respiratory syncytial virus infection	0	1 (0.2)	0
Scrub typhus	0	0	1 (0.2)
Sepsis	1 (0.2)	0	1 (0.2)
Sinusitis	2 (0.3)	0	0
Upper respiratory tract infection	1 (0.2)	0	0
Urinary tract infection	0	2 (0.3)	1 (0.2)

PT	Brensocatib 10 mg QD (N = 663) n (%)	Brensocatib 25 mg QD (N = 663) n (%)	Placebo (N = 648) n (%)
Viral infection	0	1 (0.2)	1 (0.2)
Wound infection fungal	0	0	1 (0.2)

Source: ISS Table 1.5.1-4
Note: Patients may have more than 1 severe event within the same PT

The incidence of pneumonia in the pooled safety analysis for both brensocatib treatment groups was lower than placebo (Table 10). The pneumonia adverse events were mostly moderate in severity and deemed not related to study treatment. Severe pneumonia events are included in Table 9.

Overall, pneumonia serious adverse events (SAEs) were less frequent in the brensocatib 10 mg and 25 mg groups compared with placebo for the majority of pneumonia PTs. The more frequent serious pneumonia event by PT was pneumonia (11 [1.7%], 17 [2.6%], and 19 [2.9%] for brensocatib 10 mg, brensocatib 25 mg, and placebo groups, respectively). All other pneumonia SAEs were reported in 1 or 2 participants: pneumonia bacterial (0, 1 [0.2%], and 2 [0.3%]), pneumonia necrotizing (0, 1 [0.2%],and 0), pneumonia pseudomonal (0, 1 [0.2%], and 0), pneumonia aspiration (0, 0, 2 [0.3%]), pneumonia influenzal (0, 0, 1 [0.2%]), pneumonia pneumococcal (0, 0, and 2 [0.3%]), and eosinophilic pneumonia (0, 1 [0.2%], and 0) (ISS Table 1.5.1-6 and Table 1.5.1-2b). Pneumonia events resulted in treatment interruption for 18 participants (3, 8, and 7 in the brensocatib 10 mg, brensocatib 25 mg, and placebo groups, respectively) and treatment discontinuation for 6 participants (1, 2, and 3). Two pneumonia events were fatal (both for PT pneumonia, 1 in the brensocatib 25 mg group and 1 in the placebo group in Study INS1007-301, both deemed not related to study treatment).

Table 10: Pneumonia TEAEs in Studies INS1007-301 and INS1007-201 (Safety Analysis Set)

System Organ Class Preferred Term	Brensocatib 10 mg QD (N = 663) n (%) m	Brensocatib 25 mg QD (N = 663) n (%) m	Pooled Brensocatib (N = 1326) n (%) m	Placebo (N = 648) n (%) m
Participants with at least one pneumonia event, n (%) m EAIR	24 (3.6) 35 3.905	32 (4.8) 44 5.302	56 (4.2) 79 4.597	37 (5.7) 51 6.276
Risk difference brensocatib vs placebo (%)	-2.0900	-0.8833	N/A	N/A
Exact 95% confidence interval	-4.4960, 0.2073	-3.3953, 1.5764	N/A	N/A
Infections and infestations	**24 (3.6) 35**	**31 (4.7) 43**	**55 (4.1) 78**	**37 (5.7) 51**
Pneumonia	24 (3.6) 35	27 (4.1) 37	51 (3.8) 72	31 (4.8) 42
Pneumonia bacterial	0	2 (0.3) 2	2 (0.2) 2	3 (0.5) 3
Pneumonia necrotising	0	1 (0.2) 1	1 (0.1) 1	0
Pneumonia pneumococcal	0	1 (0.2) 2	1 (0.1) 2	1 (0.2) 1
Pneumonia pseudomonal	0	1 (0.2) 1	1 (0.1) 1	0

System Organ Class Preferred Term	Brensocatib 10 mg QD (N = 663) n (%) m	Brensocatib 25 mg QD (N = 663) n (%) m	Pooled Brensocatib (N = 1326) n (%) m	Placebo (N = 648) n (%) m
Beta haemolytic streptococcal infection	0	0	0	1 (0.2) 1
Pneumonia aspiration	0	0	0	1 (0.2) 1
Pneumonia influenzal	0	0	0	1 (0.2) 1
Pulmonary tuberculosis	0	0	0	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	0	1 (0.2) 1	1 (0.1) 1	0
Eosinophilic pneumonia	0	1 (0.2) 1	1 (0.1) 1	0

Source: ISS Table 1.5.1-6, 1.5.1-8a (Module 2.7.4 Table 19 and Table 22)
Participants are counted once within same preferred term.
EAIR = 100 × [number of patients with events] / [total time at risk]
EAIR = exposure adjusted incidence rate; m = number of events; MedDRA = medical dictionary for regulatory affairs; n = number of participants experiencing events; N/A = not applicable; QD = once daily; TEAE = treatment emergent adverse event.

Severe infections and pneumonia were deemed a potential risk based on a mechanistic theory alone, which has not been supported with evidence to date. The clinical impact of the TEAEs was minimal in relation to the severity of the indication, with low incidence of severe events with brensocatib and lower incidence than with the placebo group. Severe infections/pneumonia are not considered potential risks for the target population. Any reported adverse events will be followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

No identified risks are considered important for inclusion in the list of safety concerns.

Important potential risk: Embryo-foetal toxicity

Risk-benefit impact:

In animal embryo-foetal toxicity studies, minor skeletal anomalies of bent scapula and wavy ribs were observed in rat foetuses exposed to brensocatib. The clinical significance of these findings in humans is uncertain, but the possibility of congenital anomaly/birth defect cannot be excluded. There are no clinical data on the use of brensocatib in pregnant women. Brensocatib therapy is not recommended during pregnancy and in women of childbearing potential not using contraception, but any such exposures will be subject to routine pharmacovigilance monitoring.

Missing information: Use during breast-feeding

Risk-benefit impact:

There is no information regarding the presence of brensocatib and/or its metabolite(s) in human milk. As a risk to the newborns/infants cannot be excluded, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from brensocatib therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Missing information: Long-term safety (in particular the risk for infections and malignancies)

Risk-benefit impact:

Experience beyond 52 weeks is limited since the treatment period in the Phase 3 Study INS1007-301 was 52-weeks. In an ongoing Expanded Access Programme (EAP) [NCT05344508/INS1007-EAP]) through the cutoff date of 11 January 2025, the average length of exposure was 954 days (2.61 person-years) for the 23 participants on brensocatib 25 mg/day and 432 days (1.18 person-years) for the 463 participants on brensocatib 10 mg/day. The safety profile observed in the EAP remains consistent with the clinical data described in this document (Brensocatib Report of Safety Information from the EAP). Available non-clinical and clinical data to-date have not indicated immunotoxic or carcinogenic risk. However, the mechanism of action of brensocatib indirectly impacts proinflammatory cytokine pathways, and therefore the potential long-term risks for infections and malignancies cannot be excluded and may emerge only after prolonged exposure.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

No identified risks are considered important for inclusion in the list of safety concerns.

Important potential risk: Embryo-foetal toxicity

Potential mechanisms:

Brensocatib, a DPP-1 inhibitor, blocks activation of NSPs. Its role in the developmental process has not been established. Currently, there is no data that describes how the administration of brensocatib could lead to embryo-foetal toxicity.

Evidence source(s) and strength of evidence:

Although no major anomalies were identified in animal embryo-foetal toxicity studies, minor skeletal anomalies of bent scapula and wavy ribs were observed in rat foetuses exposed to brensocatib. The available literature supports these minor anomalies could be variations, not adverse findings (Kimmel 2014). There are no clinical data on the use of brensocatib in pregnant women. The clinical significance of the animal study findings in humans is uncertain, but the potential embryo-foetal toxicity cannot be excluded.

Characterisation of the risk:

There has not been any brensocatib exposure in pregnant women. No embryo-foetal toxicity has been reported in humans.

Risk factors and risk groups:

Women of childbearing potential.

Preventability:

Warning against the use of brensocatib during pregnancy and in women of childbearing potential not using contraception.

Impact on the risk-benefit balance of the product:

There are no clinical data on the use of brensocatib in pregnant women. Brensocatib therapy is not recommended during pregnancy and in women of childbearing potential not using contraception. The currently available data has no impact on the benefit risk balance of brensocatib.

Public health impact:

Although the annual incidence of NCFBE was 1.1- to 1.5-fold higher in women than in men across all age groups, it remained substantially lower during childbearing age (2 per 100,000 persons aged 18–34 years) compared with 154 per 100,000 persons in individuals aged ≥75 years (Weycker 2017). Given that brensocatib is indicated for a subset of NCFBE patients with 2 or more exacerbations in the prior 12 months, the number of patients at risk of pregnancy is expected to be further reduced. In addition, the use of brensocatib is not recommended during pregnancy and in women of childbearing potential not using contraception. Therefore, the potential public health impact is low.

SVII.3.2. Presentation of the missing information

Missing information: Use during breast-feeding

Evidence source:

There is no information regarding the presence of brensocatib and/or its metabolite(s) in human milk, the effects on the breastfed infant, or the effects on milk production after administration of brensocatib. Available data in animals have suggested excretion of brensocatib in breastmilk (Module SII).

Population in need of further characterisation:

Any reports of exposure to brensocatib during breast-feeding will be followed up to outcome in accordance with routine pharmacovigilance activities.

Missing information: Long-term safety (in particular the risk for infections and malignancies)

Evidence source:

The treatment period in the Phase 3 Study INS1007-301 is 52-weeks in duration. Therefore, experience beyond 52 weeks is limited (SVII.1.2.).

Population in need of further characterisation:

Additional data beyond 52 weeks will be monitored using routine pharmacovigilance activities and long-term safety will be discussed in the Periodic Safety Update Reports (PSURs). Long-term safety, including risks for infection and malignancies with prolonged exposure to brensocatib, will be monitored in a post-authorisation safety study (PASS), see Section III.2III.2III.2.

Part II: Module SVIII - Summary of the safety concerns

Table 11: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	Use during breast-feeding
	Long-term safety (in particular the risk for infections and malignancies)

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will include adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

PASS Summary

Study short name and title:

Long-term safety PASS (study title to be determined [TBD])

Rationale and study objectives:

The PASS is to evaluate long-term safety data of NCFBE patients treated with BRINSUPRI, in particular the risk for infections and malignancies.

The objective of the study is to evaluate the long-term safety profile of BRINSUPRI, including the incidence and risk of malignancies and severe infections in the treatment of NCFBE patients in the real-world setting.

Study design:

Single-arm, open-label, observational, non-interventional cohort study on NCFBE patients treated with BRINSUPRI. Each patient will be followed for up to approximately five years.

Study population:

The target study population consists of NCFBE patients initiating BRINSUPRI in European countries. The intended sample size is 1,000 participants. The recruitment will be conducted in collaboration with the European Bronchiectasis Registry (EMBARC) investigator network. Safety outcomes will be evaluated by comparison with carefully matched historical or external cohorts, which may be sourced from EMBARC, other high-quality registries, electronic health records, or claims databases.

Milestones:

- Submission of draft protocol: Quarter (Q) 3 2026
- Start of data collection: Q1 2027
- Interim analysis update report: Q4 2031 (when 500 subjects enrolled and having completed 2 years of follow up)
- Final study report: Q4 2034

III.3 Summary Table of additional Pharmacovigilance activities

Table 12: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Long-term safety PASS (study title TBD) Planned	To evaluate long-term safety, in particular risks for infections and malignancies in patients treated with brensocatib in the real-world setting	- Long-term safety - Long-term risk for infections - Long-term risk for malignancies	Submission of draft protocol	Q3 2026
			Start of data collection	Q1 2027
			Interim analysis update report	Q4 2031
			Final study report	Q4 2034

Part IV: Plans for post-authorisation efficacy studies

Table 13: Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations.

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 14: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Potential Risk: Embryo-foetal toxicity	Routine risk communication: *SmPC section 4.6* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.6* *Brensocatib is not recommended during pregnancy and in women of childbearing potential not using contraception.* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Prescription only medicine*
Missing Information: Use during breast-feeding	Routine risk communication: *SmPC section 4.6.* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from brensocatib therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Prescription only medicine*
Missing Information: Long-term safety (in particular the risk for infections and malignancies)	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Prescription only medicine*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 15: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: Embryo-foetal toxicity	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information: Use during breast-feeding	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information: Long-term safety (in particular the risk for infections and malignancies)	Routine risk minimisation measures: *None* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Long-term safety PASS (study title TBD)*

Part VI: Summary of the risk management plan

Summary of risk management plan for BRINSUPRI (brensocatib)

This is a summary of the risk management plan (RMP) for BRINSUPRI. The RMP details important risks of BRINSUPRI, how these risks can be minimised, and how more information will be obtained about BRINSUPRI's risks and uncertainties (missing information).

BRINSUPRI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how BRINSUPRI should be used.

This summary of the RMP for BRINSUPRI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BRINSUPRI's RMP.

I. The medicine and what it is used for

BRINSUPRI is authorised for the treatment of non-cystic fibrosis bronchiectasis (NCFBE) in patients 12 years of age and older with two or more exacerbations in the prior 12 months (see SmPC for the full indication). It contains brensocatib as the active substance and it is given orally.

Further information about the evaluation of BRINSUPRI’s benefits can be found in BRINSUPRI’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise these risks

Important risks of BRINSUPRI, together with measures to minimise such risks and the proposed studies for learning more about BRINSUPRI's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BRINSUPRI is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of BRINSUPRI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BRINSUPRI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	Use during breast-feeding
	Long-term safety (in particular the risk for infections and malignancies)

II.B Summary of important risks

Important potential risk: Embryo-foetal toxicity	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6* *PL section 2* Additional risk minimisation measures *None*

Missing information: Use during breast-feeding	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6* *PL section 2* Additional risk minimisation measures *None*

Missing information: Long-term safety (in particular the risk for infections and malignancies)	
Risk minimisation measures	Routine risk minimisation measures *None* Additional risk minimisation measures *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BRINSUPRI.

II.C.2 Other studies in post-authorisation development plan

Long-term safety PASS (study title TBD)

Purpose of the study:

A single arm, open label, observational, non-interventional cohort study to evaluate long-term safety data of NCFBE patients treated with BRINSUPRI, in particular the risk for infections and malignancies.

Part VII: Annexes

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List of Annex Tables

Annex 4: Specific adverse drug reaction follow-up forms

None.

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.