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

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1. To evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs) over the 52-week treatment period

Ethical review	Approved WMO
Status	Completed
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON54326

Source
ToetsingOnline

Brief title
The ASPEN Study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Bronchiectasis, Chronic inflammatory lung disease

Research involving
Human

Sponsors and support

Primary sponsor: Insmed Incorporated
Source(s) of monetary or material Support: Pharmaceutical Company: Insmed Incorporated

Intervention

Keyword: Brensocatib, Bronchiectasis, Fibrosis, NCFBE

Outcome measures

Primary outcome

Rate of adjudicated pulmonary exacerbations over the 52 week treatment period

Secondary outcome

1. Time to first adjudicated PE over the 52-week treatment period

2. Proportion of subjects who are exacerbation free over the 52-week treatment

period

3. Change from Baseline in postbronchodilator forced expiratory volume in 1

second (FEV1) at Week 52.

4. Rate of severe adjudicated PEs over the 52-week treatment period.

5. Change in QOL-B, Respiratory Symptoms Domain Score from Baseline to Week 52

in adult subjects.

6. Incidence and severity of treatment-emergent adverse events and other safety

variables (eg, clinical laboratory test results, vital signs and ECG.

Study description

Background summary

Non-cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis) is a chronic inflammatory disease defined by permanent dilatation of the bronchi (Barker, 2002). Subjects suffer from daily cough and sputum production and experience frequent exacerbations. The prevalence of NCFBE has steadily increased over the past 10 years in both the United States and Europe (Henkle et al., 2018; Quint et al., 2016). Despite an urgent need for treatment that can break the cycle of inflammation, infection, and irreversible progressive lung damage, there are no approved therapies specifically targeting this disease.

Subjects with NCFBE experience pulmonary exacerbations with an average frequency ranging from 1.5 to 6 per year (Chalmers et al., 2014; Goeminne PC, 2014), and have poor quality of life. Frequent exacerbations of bronchiectasis are independently associated with worse quality of life, decreased lung function, and substantial morbidity and mortality (Barker, 2002; Chalmers et al., 2018; Quittner et al., 2015).
Inflammation in bronchiectasis is dominated by neutrophils (Chalmers, 2017; Finch et al., 2019). Activation of neutrophils in the airway leads to release of NSPs, including NE, which is believed to be central to the pathophysiology of bronchiectasis (Chalmers and Chotirmall, 2018). Elevated NE, PR3, and CatG overwhelm natural inhibitors, such as alpha-1 antitrypsin and secretory leukoproteinase inhibitor (Dubois et al., 2012; Sibila et al., 2019), which leads to damaged airway walls (Chalmers and Chotirmall, 2018), mucus hypersecretion (Voynow et al., 1999), exacerbated inflammation (Finch et al., 2019), and disabled neutrophil and macrophage functions, increasing the risk of infection. NSPs are activated during neutrophil maturation in the bone marrow through the action of the enzyme DPP1, also known as cathepsin C. DPP1 removes the N terminal dipeptide sequence of NSPs, allowing active enzymes to be packaged into granules prior to release into the circulation (Palmer et al., 2018).
There is currently no therapy approved by regulatory authorities in the United States or Europe for the treatment of NCFBE. The primary goal of treatment is to treat the underlying cause, prevent disease progression, maintain or improve lung function, and improve the symptoms and quality of life.

Brensocatib ((2S)-N-{(1S)-1-cyano-2- [4-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl) phenyl] ethyl -1,4-oxazepane-2-carboxamide monohydrate) is a highly potent, selective, small molecule competitive and reversible inhibitor of DPP1 that is currently being developed for the treatment of NCFBE. Brensocatib (developed under the investigational product code INS1007) has been shown to inhibit NSP activity in blood in animal models and in healthy volunteers after 2 weeks to 1 month of dosing (Palmer et al., 2018). Treatment with brensocatib could therefore reduce neutrophilic inflammation in the systemic circulation and the lungs, leading to reduced risk of exacerbations in patients with NCFBE. Studies with naïve and lipopolysaccharide-induced pulmonary inflammation models in the rat showed that DPP1 inhibition with oral brensocatib translates well in vivo, as significant decreases in the activities

of NSPs were observed.

Study objective

1. To evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs) over the 52-week treatment period

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study to assess the efficacy, safety, and tolerability of two dosage strengths of brensocatib compared with placebo in subjects with non-cystic fibrosis bronchiectasis (NCFBE). A total of 1,620 subjects will be randomized in a 1:1:1 ratio to 3 treatment arms (540 subjects per arm) to receive brensocatib 10 mg once daily (QD), brensocatib 25 mg QD, or matching placebo QD for 52 weeks. Randomization will be stratified based on geographic region (North America, Europe, Japan, and the Rest of the World), screening sputum sample positive or negative for Pseudomonas aeruginosa, and the number of prior pulmonary exacerbations (2, or >=3) in the previous 12 months. In addition, randomization will be enforced to have at least 30% of subjects with 3 or more prior pulmonary exacerbations (PEs) and to have no more than 20% of subjects older than 75 years of age.
This study will also comprise a pharmacokinetic/pharmacodynamic (PK/PD) substudy (n*300 subjects) and a computed tomography (CT) scan substudy (n*225 subjects).

Intervention

Approximately 1,660 subjects will be randomly assigned to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD for 52 weeks.

Study burden and risks

The investigator will:
- Ask about your medical history - at one visit
- Ask about your physical health, side effects, smoking status and any medications you have taken since your last visit - at each visit
o For your safety, it is important to give complete and accurate information.

- Perform a Computed Tomography (CT) scan of your lungs to evaluate the presence of NCFBE, only if a scan has not been performed in the past 5 years. If the CT scan cannot be read by the reviewers due to quality issues, a new CT scan will be performed.

- Do a physical examination and measure your: height and weight - at one visit.

- Measure your vital signs: temperature, blood pressure, heart rate and lung functions - at every in-clinic visit.
- Collect urine for laboratory testing, approximately 5 mL of urine is needed - at 7 visits.
o A urine pregnancy test is done if you can get pregnant - at 10 visits.

- Collect blood for laboratory testing, approximately 8 mL of blood is taken - at 7 visits.
o A blood pregnancy test is done if you can get pregnant - at one visit (visit 2).
o During the entire study, approximately 64 mL of blood will be collected from you.

- Perform an electrocardiogram (ECG) - at 5 visits
- Perform lung function tests - at 5 visits

- Give you 3 electronic questionnaires. You will be provided with an electronic device for entering responses to the study questionnaires. This device will come complete with data plan for internet access.

o Bronchiectasis Exacerbation and Symptoms Tool (BEST)
* You will be asked to complete it daily until week 56 (visit 12).
* It takes about 2 minutes to fill out this questionnaire.

o Quality of Life Questionnaire-Bronchiectasis (QOL-B)
* You will be asked to complete it for the first time at Visit 2, and then you will complete this questionnaire every 2 weeks.
* It takes about 10 minutes to fill out this questionnaire.

o EuroQoL-5D-5L (EQ-5D-5L)
* You will be asked to complete it - at 7 visits.
* It takes about 5 minutes to fill out this questionnaire.

- Assess your oral/dental health - at 11 visits
- Explain dental hygiene - at 11 visits.
- Assess pulmonary exacerbation. The study doctor will check if you had any worsening of your NCFBE that would count as a *pulmonary exacerbation* - at 11 visits.
- Assess your skin condition - at 7 visits.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For Adults subjects :
1. Provide their signed study informed consent to participate.
2. Male or female >=18 years and <=85 years of age (inclusive) at screening.
3. BMI >=18.5 at screening.
4. Clinical history consistent with NCFBE (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).
a. For each subject, the most recent chest CT scan (but not older than 5 years before the Screening date) will be selected for transfer to the central reading facility for confirmation of the diagnosis of NCFBE.
b. If the CT scan cannot be read by the reviewers due to quality issues, a new high-resolution CT scan will be performed.
c. In case a chest CT Scan in the last 5 years is not available, a new chest CT scan must be obtained for confirmation of the diagnosis of NCFBE by the central reading facility.
5. Postbronchodilator FEV1 at the Screening Visit >=30% of predicted normal value, calculated using National Health and Nutrition Examination Survey

reference equations and must have an absolute value >=750 mL.
6. Current sputum producer with a history of chronic expectoration of at least 3 months in the past 12 months, and able to provide sputum sample during screening (Visit 1). If a subject is unable to produce sputum spontaneously during screening, the subject will be considered a screen failure. The subject should not undergo a sputum induction procedure during screening to meet inclusion criterion.
7. Mucopurulent or purulent sputum color assessed at the Screening Visit by color chart developed by MP Murray (Murray et al., 2009).
8. At least 2 pulmonary exacerbations defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before the Screening Visit.
9. Women must be post-menopausal (defined as no menses for 12 months without an alternative medical cause), surgically sterile, or using highly effective double barrier contraception (ie, methods that in combination achieve <1% unintended pregnancy rates per year) from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner. For women <=45 years of childbearing potential, an additional confirmatory testing of FSH level with a threshold of >40 mIU/mL should be performed to be considered infertile.
Note: Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual lifestyle of a subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
10. Male subjects with female partners of childbearing potential must be using effective contraception from Day 1 to at least 90 days after the last dose. Acceptable methods include true abstinence (refraining from intercourse during the study), combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone- releasing systems.
11. Male subjects with pregnany or non-pregnant WOCBP partners must use condoms to avoid potential exposure to the embryo/fetus.

Exclusion criteria

1. A primary diagnosis of COPD or asthma as judged by the Investigator. Patients with comorbid COPD and/or asthma can be enrolled if bronchiectasis is their primary diagnosis
2. Subjects receiving supplemental oxygen >12 hours per day.
3. Bronchiectasis due to cystic fibrosis.

4. Current smokers as defined per CDC.
5. No evidence of bronchiectasis according to the BE-CT scoring system.
6. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the investigator.
7. Known history of HIV infection.
8. Established diagnosis of hepatitis B viral infection at the time of screening, or positive for HBsAg at the time of screening.
Subjects who have gained immunity for hepatitis B virus infection after vaccination (subjects who are HBsAg-negative, HBsAb-positive, and HBcAb-negative are eligible for the study).
Subjects with positive HBcAb are eligible for the study only if hepatitis B virus DNA level is undetectable.
9. 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.
10. Currently being treated for NTM lung infection, allergic bronchopulmonary aspergillosis, or TB.
11. Active and current symptomatic infection by COVID-19.
12. 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.
13. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).
14. Receiving medications or therapy that are prohibited as concomitant medications (see Section 5.3 for prohibited concomitant medications)
15. Started oral or inhaled antibiotics as chronic treatment for NCFBE for <3 months prior to the Screening visit.
a. Subjects on antibiotics as chronic treatment should be on such treatment for at least 3 months prior to enrollment while meeting all other inclusion criteria and none of the exclusion criteria.
16. Chronic treatment with oral steroids (irrespective of the indication), is prohibited
17. Subjects who have adjustments to their baseline medications within 1 month before Screening; they can be rescreened a month after the new treatment has been initiated.
18. Abnormal renal function test result eGRF <30 mL/min by Chronic Kidney Disease - Epidemiology Collaboration equation formula) at Screening.
19. Active liver disease or hepatic dysfunction manifested as follows:
a. Elevated liver function test results (ALT or AST >3 × ULN).
b. Total Bilirubin >2 × ULN (isolated bilirubin >2 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones.

d. Child-Pugh class C
20. History of malignancy in the past 5 years, except completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
21. Previously participated in a clinical trial of brensocatib.
22. An absolute neutrophil count <1,000/mm3 at the Screening Visit.
23. Received any live attenuated vaccine within 4 weeks prior to the first administration of brensocatib. 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.
24. Significant hemoptysis (>=300 mL or requiring blood transfusion) within 6 weeks prior to the Screening Visit or during the Screening Period.
25. Have diagnosed periodontal disease and are either:
a. Currently treated by a dentist for this condition or
b. Are expected to have periodontal disease-related procedures within the study period.
26. Suffering an exacerbation 4 weeks before Screening or during the Screening period. In this case, subjects will be considered a screen failure. Subjects are eligible for rescreen only after recovery and 4 weeks after last dose of antibiotic treatment.
27. Unable to comply with >=75% of completion of electronic diary entries or have compliance issues during the Screening Period.
28. Participated in any other interventional clinical studies within 3 months before Screening Visit.
29. Clinical diagnosis of Papillon-Lefevre Syndrome.
30. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the subject's participation in the study. Examples include but are not limited to short life expectancy, uncontrolled diabetes, cardiovascular conditions (eg, NYHA Class III or IV cardiac failure), severe renal conditions (eg, severe nephrotic syndrome), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinologic, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for subjects excluded under this criterion will be noted in study documents (chart notes, CRF, etc.).
31. Any clinically significant abnormal laboratory values at Screening or diseases or disorders (eg, survivors of severe COVID-19 disease including ARDS, cardiovascular, pulmonary, gastrointestinal, liver, kidney, neurological, musculoskeletal, endocrine, metabolic, psychiatric, physical impairment, or a lung transplantation) that, in the opinion of the Investigator, may put the subject at risk by participating in the study, or interfere with the subject's treatment, assessment, or influence the results of the study, or have compliance issues with the study or have a planned or anticipated major surgical procedure during the study.
32. History of alcohol or drug abuse within 6 months prior to the Screening Visit.

33. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study subject as a result of his/her participation in this clinical trial, may make subject*s participation unreliable, or may interfere with study assessments. The specific justification for subjects excluded under this criterion will be noted in study documents.
34. Is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	08-07-2021
Enrollment:	27
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INS1007
Generic name:	brensocatib

Ethics review

Approved WMO Date:	29-10-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2022

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-05-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	2020-001643-13
EudraCT	EUCTR2020-003688-25-NL
CCMO	NL75434.028.20