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Newcastle University

Health Technology Briefing
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Brensocatib for people aged 12 and over with non-cystic fibrosis bronchiectasis

Company/Developer	Insmed Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26962	NICE ID: Not available	UKPS ID: 668033

Licensing and Market Availability Plans

Currently in phase II/III clinical development.

Summary

Brensocatib is currently in clinical development for the treatment on non-cystic fibrosis bronchiectasis in patients aged 12 and older. Bronchiectasis is a lung condition where inflammation from lung infections causes irreversible damage to the lungs which can get worse over time. During bronchiectasis, the airways are wider and become inflamed with thick phlegm (sputum). This means the airways may not clear properly. Too much phlegm can cause bacterial infections, which can lead to chest infections. Chest infections should be treated quickly to stop lung damage. Symptoms of the condition include repeated infections, coughing up excess sputum, chest pain, and shortness of breath. There are currently limited treatment options for non-cystic fibrosis bronchiectasis, with the main treatment being for the frequent infection's that patients experience.

Brensocatib works by inhibiting a protein created by the immune system, dipeptidyl peptidase 1 (DPP1), when it is trying to fight infection. By inhibiting the activity of DPP1, brensocatib should reduce the amount of activated immune cells, and reduce inflammation. Brensocatib is administered orally. If licensed, brensocatib will provide a new treatment option for patients with non-cystic fibrosis bronchiectasis who currently have few options available.

Proposed Indication

Treatment of non-cystic fibrosis bronchiectasis in patients aged 12-85[1]

Technology

Description

Brensocatib (INS1007), is a novel oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1).[2] DPP1 is an enzyme responsible for activating neutrophil serine proteases (NSPs), such as neutrophil elastase, in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active NSPs that cause lung destruction and inflammation.[3]

Brensocatib is currently in phase II/III clinical development for the treatment on non-cystic fibrosis bronchiectasis in patients aged 12 to 85 years (NCT03218917 (WILLOW), NCT04594369 (ASPEN)).[1,4] In the phase III trial, ASPEN, brensocatib is administered orally in 10mg or 25mg tablets once daily for 52 weeks [1] In the completed phase II trial, WILLOW, brensocatib was administered orally in 10mg or 25mg tablets once daily for 24 weeks.[4]

Key Innovation

Brensocatib may decrease the damaging effects of inflammatory diseases such as non-cystic fibrosis bronchiectasis by inhibiting DPP1 and its activation of NSPs.[3] Current therapies only treat the symptoms rather than the underlying causes. The WILLOW trial showed a reduction of neutrophil serine protease activity with brensocatib in patients with bronchiectasis was associated with improvements in bronchiectasis clinical outcomes.[5] If licensed, brensocatib will offer a new treatment option for patients who have few targeted treatments available.

Regulatory & Development Status

Brensocatib does not currently have marketing authorisation in the EU/UK for any indication.

Brensocatib is currently in phase II/III clinical development for the treatment of COVID-19[6]
and chronic rhinosinusitis without nasal polyps.[7]

Brensocatib has the following regulatory designations/awards:

- a PRIME status for the treatment of non-cystic fibrosis bronchiectasis by the European Medicines Agency (EMA) in November 2020[8]
- a Breakthrough Therapy by the United States Food and Drug Administration (FDA) for non-cystic fibrosis bronchiectasis in June 2020[9]

Patient Group

Disease Area and Clinical Need

Bronchiectasis is a long-term condition where the airways of the lungs become widened, leading to a build-up of excess mucus that can make the lungs more vulnerable to infection.[10] For most people, inflammation from an infection in the lungs will pass without causing any further problems, but bronchiectasis can occur if the inflammation permanently destroys the elastic-like tissue and muscles surrounding the bronchi

(airways), causing them to widen. Further infections cause more inflammation which further increases the irreparable damage.[11] The most common symptom of bronchiectasis is a persistent cough that brings up a large amount of phlegm daily. Other symptoms include: shortness of breath, wheezing, coughing up blood or bloodstained phlegm, chest pain, joint pain, and clubbing of the fingertips.[12] In around half of all cases of bronchiectasis, no obvious cause can be found. However, the known causes are; pneumonia, tuberculosis, whooping cough, measles, damage in the lung from breathing in a small object, primary ciliary dyskinesia, a weak immune system, inflammatory bowel disease, rheumatoid arthritis, acid reflux, and allergic bronchopulmonary aspergillosis. It's more common in women than in men and around 60% of people diagnosed with bronchiectasis are over 70 years old. [11,13] Bronchiectasis is sometimes called non-cystic fibrosis bronchiectasis. This is because bronchiectasis and cystic fibrosis have similar symptoms. However, the treatment and outlook are different for both conditions.[13]

Around 1 in 200 adults in the UK have bronchiectasis.[13] In England (2022-23), there were 21,102 finished consultant episodes (FCE) and 11,497 admissions for bronchiectasis (ICD-10 code: J47), which resulted in 77,578 FCE bed days and 2,712 day cases.[14]

Recommended Treatment Options
The National Institute for Health and Care Excellence (NICE) recommends the antibiotics amoxicillin, doxycycline and clarithromycin to treat acute exacerbations of bronchiectasis in adults and children.[15]

Clinical Trial Information

Trial	**ASPEN; NCT04594369, EudraCT2020-003688-25;** 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. **Phase III** - Active, not recruiting **Locations:** 15 EU countries, UK, USA, Canada, and other countries **Primary completion date:** March 2024
Trial Design	Randomised, parallel assignment, double masked, placebo-controlled
Population	N=1767 (actual); patients aged 12-85 years with a clinical history consistent with non-cystic fibrosis bronchiectasis that is confirmed by chest computerised tomography (CT) scan.
Intervention(s)	Brensocatib (10mg or 25mg, orally administered once daily for 52 weeks)
Comparator(s)	Matched placebo (orally administered once daily for 52 weeks)
Outcome(s)	Primary outcome measures: • Rate of adjudicated pulmonary exacerbations (PEs) [Time frame: 52 weeks] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**WILLOW;** NCT03218917, EudraCT 2017-002533-32**.** Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety & Tolerability, and PK of INS1007 Administered Once Daily for 24 Weeks in Subjects With Non-CF Bronchiectasis - The Willow Study. **Phase II -** Completed **Locations:** 8 EU countries, UK, USA, and other countries **Study completion date:** December 2019
Trial Design	Randomised, parallel assignment, quadruple masked, placebo-controlled
Population	N=256 (actual); adults aged 18-85 with a clinical history of non-cystic fibrosis bronchiectasis.
Intervention(s)	Brensocatib (10mg or 25mg orally administered once daily for 24 weeks)
Comparator(s)	Matched placebo (orally administered once daily for 24 weeks)
Outcome(s)	Primary outcome measures: • Time to first pulmonary exacerbation over 24-week treatment period [Time frame: Baseline (day 1) to week 24] See trial record for full list of outcomes.
Results (efficacy)	Brensocatib treatment prolonged the time to the first exacerbation as compared with placebo (P = 0.03 for 10-mg brensocatib vs. placebo; P = 0.04 for 25-mg brensocatib vs. placebo). The adjusted hazard ratio for exacerbation in the comparison of brensocatib with placebo was 0.58 (95% confidence interval [CI], 0.35 to 0.95) in the 10-mg group (P = 0.03) and 0.62 (95% CI, 0.38 to 0.99) in the 25-mg group (P = 0.046). The incidence-rate ratio was 0.64 (95% CI, 0.42 to 0.98) in the 10-mg group, as compared with placebo (P = 0.04), and 0.75 (95% CI, 0.50 to 1.13) in the 25-mg group, as compared with placebo (P = 0.17). With both brensocatib doses, sputum neutrophil elastase activity was reduced from baseline over the 24-week treatment period.[5]
Results (safety)	The incidence of dental and skin adverse events of special interest was higher with the 10-mg and 25-mg brensocatib doses, respectively, than with placebo.[5]

Estimated Cost

The cost of brensocatib is currently unknown.

Relevant Guidance

NICE Guidance

- NICE guideline. Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial processing. (NG117). December 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Respiratory. E03/S/g.

Other Guidance

- Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, et al. European Respiratory guidelines for the management of adult bronchiectasis. 2017.[16]
- Pasteur MC, Bilton D, Hill AT. British Thoracic Society Guideline for non-CF Bronchiectasis. 2010.[17]

Additional Information

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