Poster

Study design of a Phase II, randomized, double-blind, placebo-controlled trial of a novel cathepsin C inhibitor BI 1291583 in patients with bronchiectasis (Airleaf™)

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AIM: Describe the study design of a Phase II trial investigating the efficacy and safety of the novel cathepsin C inhibitor BI 1291583 in adult patients with bronchiectasis

BACKGROUND

- Bronchiectasis is characterized by the uncontrolled release of neutrophil serine proteases (NSPs), which promote inflammation, impair mucociliary clearance and damage airways, increasing the risk of pulmonary exacerbations and structural lung damage.[1,2]
- No approved treatments are available to reduce inflammation and tissue destruction in bronchiectasis.
- The cysteine protease cathepsin C (CatC, also known as dipeptidyl peptidase 1) activates NSPs such as neutrophil elastase (NE) during neutrophil maturation in the bone marrow.[3]
- BI 1291583 is a reversible, potent and selective CatC inhibitor that may ameliorate neutrophilic inflammation in the lungs by inhibiting NSP activation.[4]
- BI 1291583 has completed Phase I studies and has entered Phase II testing. For further details, please see the oral presentation on Phase I data.[5]

METHODS

Key inclusion criteria

- 18–85 years old
- Bronchiectasis confirmed by CT scan
- Current sputum producers
- History of 2 exacerbations requiring antibiotic treatment in the last 12 months OR 1 exacerbation if SGRQ symptoms score >40

Key exclusion criteria

- Recent change in dose or regimen of regular bronchiectasis treatment (stable maintenance treatment allowed)
- Exacerbation during screen
- Diagnosis of cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, alpha1-antitrypsin deficiency, allergic bronchopulmonary aspergillosis requiring treatment

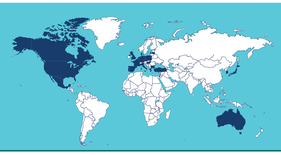
- Randomization will be stratified according to 1) positive or negative sputum culture at screening for *Pseudomonas aeruginosa* and 2) whether the patient is receiving macrolides as maintenance therapy.

Trial objectives

- Demonstrate a non-flat dose–response curve and evaluate the dose–response relationship for three oral dosing regimens of BI 1291583 versus placebo on time to first bronchiectasis exacerbation up to Week 48.
- Demonstrate superiority of BI 1291583 5 mg versus placebo on time to first pulmonary exacerbation up to Week 48 and on the rate of pulmonary exacerbations up to Week 48.

Trial timeline

March 2022 — NCT05238675 — December 2023



Airleaf™

Trial sites in 23 countries

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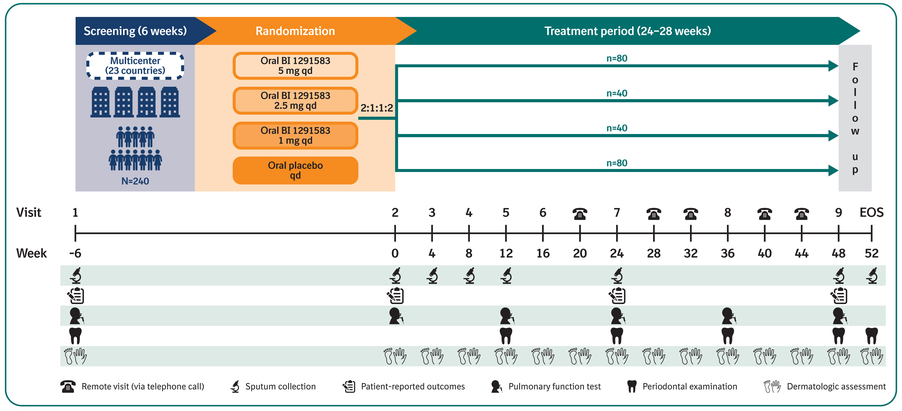
Canada	Bulgaria	Germany	Italy	Turkey	Japan
USA	Czech Republic	Greece	Latvia	Poland	South Korea
Mexico	Denmark	Hungary	Netherlands	Portugal	Australia
Belgium	France	Israel	Spain	United Kingdom	



Primary endpoint

Time to first pulmonary exacerbation up to 48 weeks, defined as ≥3 of the following symptoms for ≥48 hours + antibiotics prescription:

- ✔ ↑ Cough
- ✔ ↑ Sputum purulence
- ✔ ↑ Sputum volume or changed consistency
- ✔ Hemoptysis
- ✔ Fatigue and/or malaise
- ✔ ↑ breathlessness and/or ↓ exercise tolerance

Secondary endpoints

- Relative change from baseline in sputum NE activity at Week 12
- Rate of pulmonary exacerbations up to 48 weeks
- Absolute change from baseline at Week 24 in SGRQ symptoms score
- Absolute change from baseline at Week 24 in post-bronchodilator FEV_1% predicted
- Occurrence of an exacerbation by Week 24 after first drug administration

Efficacy assessment

Measures of disease worsening

- Pulmonary exacerbations
- Treatment with antibiotics

Sputum assessment

- NE activity
- Sputum weight

Patient-reported outcomes

- SGRQ
- Leicester Cough Questionnaire
- Cough and Sputum Assessment Questionnaire
- Quality of Life Bronchiectasis Questionnaire
- Visual Analogue Scale

Pulmonary function

- FEV_1% predicted

Safety and PK assessment

- Safety will be monitored throughout the study by adverse event reporting, physical examination, vital signs, laboratory safety parameters, 12-lead electrocardiogram, and periodontal and dermatologic assessments.
- PK analysis will be performed in blood for BI 1291583 trough plasma concentrations.

Planned statistical analyses

- The non-flat dose–response hypothesis comparing the placebo and BI 1291583 dose groups (proof-of-concept) will be evaluated using MCP-Mod techniques, controlling type I error at 0.05 (one-sided).
- If a non-flat dose response is achieved, formal statistical testing of the time to first pulmonary exacerbation and the rate of pulmonary exacerbations will be performed in a hierarchical way for the comparison of BI 1291583 5 mg versus placebo (each at one-sided alpha of 0.025).
- Exploratory interim analyses are planned to assess the pharmacodynamic response of BI 1291583.

CONCLUSION

- The **Airleaf™** trial will provide information on the efficacy, safety and optimal dosing regimen of BI 1291583 in preventing pulmonary exacerbations, by reducing neutrophilic inflammation in patients with bronchiectasis.

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INTERACTIVE

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Abbreviations

CatC, cathepsin C; CT, computed tomography; EOS, end of study; FEV_1, forced expiratory volume in 1 second; MCP-Mod, Multiple Comparisons Procedure – Modelling; NE, neutrophil elastase; NSP, neutrophil serine protease; PK, pharmacokinetic; qd, once daily; SGRQ, St. George's Respiratory Questionnaire; W, week.

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