A Phase 3, Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial Evaluating Repeated Courses of Aztreonam for Inhalation Solution/Aztreonam 75 mg Powder and Solvent for Nebuliser Solution in Subjects with non-CF Bronchiectasis and Gram-Negative Endobronchial Infection

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This study is designed to assess the safety and efficacy of aztreonam for inhalation solution/aztreonam 75 mg powder and solvent for nebuliser solution (AZLI) in subjects with non-CF bronchiectasis and gram-negative endobronchial infection.

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

Summary

ID

NL-OMON35895

Source
ToetsingOnline

Brief title
AZLI study AIR-BX2 (035/062; GS-US-219-0104)

Condition

- Bronchial disorders (excl neoplasms)

Synonym
bronchiectasis, permanently dilated airways

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc.

Intervention

Keyword: Aztreonam, bronchiectasis, endobronchial infection, inhalation antibiotics

Outcome measures

Primary outcome

The primary endpoint is the change in the Respiratory Symptoms score on the QOL-B from baseline to the end of placebo-controlled Course 1 (i.e., change from Day 0 [Visit 2] to Day 28 [Visit 4]).

Secondary outcome

The secondary endpoints are:

- Change in the Physical Functioning score on the QOL-B from baseline to the end of placebo-controlled Course 1 (i.e., change from Day 0 [Visit 2] to Day 28 [Visit 4])

- Change in the Respiratory Symptoms score on the QOL-B at the end of placebo-controlled Course 2 (Day 84 [Visit 6]) compared to baseline (Day 0 [Visit 2])

- Change in the Physical Functioning score on the QOL-B at the end of placebo-controlled Course 2 compared to baseline

- Time to Protocol-Defined Exacerbation (PDE) prior to open-label AZLI

treatment

Study description

Background summary

Bronchiectasis is a disease of the lungs named for its most prominent morphologic feature: irreversibly dilated central and medium-sized airways. A common pathophysiologic feature of bronchiectasis is a chronic cycle of transmural infection and inflammation. The airway becomes compromised by intrinsic defect or extrinsic insult, leading to tissue injury due either to the infectious organism directly, or mediated by the host response. The tissue injury causes further airway compromise and worsening infection, ultimately leading to more inflammation and lung damage. Regardless of the specific etiology, this *vicious cycle* is thought to underlie both the characteristic pathologic changes of bronchiectasis and its clinical sequelae.
There is strong evidence for the benefit of long-term antibiotic treatment in patients with bronchiectasis based on meta-analysis of existing clinical trials; in some cases, these trials show significant symptomatic and functional improvement, presumably as a result of the significant bacterial killing observed. However, the existing options for antibiotic maintenance therapy in patients with bronchiectasis are limited, and none has been approved specifically for this indication. Scheduled therapy with IV antibiotics is expensive, impractical, and often prone to significant risk of toxicity and development of resistance. Certain oral agents have potential for use as maintenance therapy, but their long-term safety and effectiveness in non-CF bronchiectasis are either unknown or highly suspect due to concerns about development of resistance.
AZLI is a novel formulation of aztreonam, which has been used extensively as parenteral therapy for infections caused by a wide range of gram-negative bacteria. In clinical trials, AZLI has been delivered using the eFlow® nebulizer system. The eFlow nebulizer system is a single-subject, multi-use nebulizer that uses a vibrating perforated membrane to generate an aerosol. The eFlow is an investigational device in the US and is CE marked in Europe. The eFlow is approved under the trade name Altera® in the US and the EU.
Based on the observed efficacy and safety of AZLI in an adult CF population, and the significant overlap in pulmonary pathophysiology for patients with CF and non-CF bronchiectasis, AZLI represents a potential treatment option for patients with bronchiectasis and gram-negative endobronchial infection. Results from the clinical experience with AZLI in subjects with bronchiectasis (GS-US-219-0102) also support this concept.

Study objective

This study is designed to assess the safety and efficacy of aztreonam for inhalation solution/aztreonam 75 mg powder and solvent for nebuliser solution (AZLI) in subjects with non-CF bronchiectasis and gram-negative endobronchial infection.

Study design

This is a Phase 3, double-blind, multicenter, randomized, placebocontrolled study in subjects with bronchiectasis and gram-negative endobronchial infection. The study consists of 10 scheduled visits with a total study duration of 30 weeks.
Enrolled subjects will be randomized with a 1:1 allocation to receive blinded AZLI or placebo, and will remain on the same treatment arm until the open-label portion of the study. Subjects who experience worsening respiratory signs and/or symptoms after
Visit 2 may be treated with nonstudy antibiotics at the investigator*s discretion without discontinuation from the study.
At Visit 2, subjects will begin the first of two double-blind, placebo-controlled 28-day treatment courses. Each placebocontrolled course will be followed by a 28-day off-treatment interval. After completing both placebo-controlled courses, all subjects will receive a 28-day open-label course of AZLI, returning to clinic at the end of the 28-day treatment period, and 4 and 8 weeks after the last dose of study drug.

Intervention

Two 28-day placebo-controlled treatment courses are planned, followed by one 28-day open-label course of AZLI treatment. AZLI/placebo is to be administered three times daily (TID) for 28 days per course, with a minimum of 4 hours between doses. Each dose is to be preceded by administration of a short-acting inhaled bronchodilator. AZLI will be administered via the eFlow® nebulizer system.

Study burden and risks

There will be 10 scheduled clinic visits. Planned visits include screening prior to randomization, evaluations at 14-day intervals during the first placebo-controlled course, and every 28 days subsequently.
Study procedures will include administration of the Quality of Life Questionnaire - Bronchiectasis (QOL-B) and the 6-Minute Walk Test (6MWT) during each clinic visit. Spirometry will be performed after bronchodilator administration at each scheduled visit; in addition, spirometry will be repeated after in-clinic study drug treatment at Visits 2 and 7. Sputum will be collected at every visit for microbiology assessments. Adverse events (including hospitalizations) and concomitant medication use will be assessed at every visit. Blood will be collected for standard laboratory tests at Visits 1,

2, 4, 6, 8 and 10.

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

- Male/Female >= 18 years old
- Bronchiectasis confirmed by documented computed tomography (CT) scan within 5 years prior to Visit 1, or by prior approval of the Medical Monitor without intervening lung resection
- Reported chronic sputum production on most days during the 4 weeks prior to Visit 1
- Positive sputum culture for target gram-negative organism(s) at Visit 1
- Documented history of positive sputum culture (or bronchoscopic culture) for a target gram-negative organism OR documented history of treatment with antibiotics with gram-negative coverage for an exacerbation of bronchiectasis within 5 years prior to Visit 1
- Chest X-Ray (CXR) obtained and interpreted at Visit 1 or between Visits 1 and 2, without

significant acute findings (e.g., no new infiltrate) With prior approval of the Medical Monitor, a CXR obtained within 10 days prior to Visit 1 may be acceptable for study entery.
- Forced expiratory volume in one second (FEV1) >=20% predicted approximately 15 minutes post-bronchodilator at Visit 1

Exclusion criteria

- Hospitalization within 14 days prior to Visit 1
- Reported episode of hemoptysis > 30 mL (~2 tablespoons) within 28 days prior to Visit 1, on the day of Visit 1, and from Visit 1 through Visit 2
- Antibiotics to treat respiratory symptoms (excluding chronic, stable treatment with a macrolide) within 14 days prior to Visit 1, on the day of Visit 1, and from Visit 1 through Visit 2
- Change in bronchodilator, inhaled corticosteroid, macrolide, or bronchial hygiene therapies within 28 days prior to visit 1 and through study completion.
- Change in systemic corticosteroid therapy within 28 days prior to Visit 1 and from Visit 2. After Visit 2, systemic corticosteroid therapy (maximum of 14 days per course) will be allowed to treat worsening respiratory signs and/or symptoms.
- Previous treatment with or exposure to Cayston® (AZLI)
- Serious adverse event between Visits 1 and 2
- History of cystic fibrosis (CF)
- Current treatment for nontuberculous mycobacteria (NTM) infection
- Active mycobacterium tuberculosis (MTB) infection within one year prior to Visit 1

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: Recruitment stopped

Start date (anticipated):	02-04-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cayston
Generic name:	Aztreonam 75 mg powder and solvent for nebuliser solution

Ethics review

Approved WMO Date:	07-06-2011
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	10-02-2012
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-05-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	27-02-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	14-05-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	11-06-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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
EudraCT	EUCTR2010-023959-28-NL
ClinicalTrials.gov	NCT01314716
CCMO	NL36935.094.11