A Phase 1b/2a, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Nebulized Bacteriophage Treatment in Outpatient Adult Cystic Fibrosis (CF) Subjects with Chronic Pseudomonas aeruginosa (PsA) Pulmonary Infection

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Primary Objective:To evaluate the safety and tolerability of nebulized BX004-A in CF subjects with chronic PsA pulmonary infection.Exploratory Objective:To evaluate the effect of BX004-A on sputum PsA burden, lung function, frequency of APEs, and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53309

Source
ToetsingOnline

Brief title
BMX-04-001

Condition

- Respiratory disorders congenital
- Viral infectious disorders
- Respiratory tract infections

Synonym
Chronic Pseudomonas aeruginosa Pulmonary Infection, cystic fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: BiomX Ltd.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Bacteriophage Treatment, Cystic Fibrosis, Nebulized, Pseudomonas Aeruginosa

Outcome measures

Primary outcome

The safety and tolerability of nebulized BX004-A in CF subjects with chronic

PsA pulmonary infection.

Secondary outcome

The effect of BX004-A on sputum PsA burden, lung function, frequency of APEs,

and quality of life at various timepoints.

Study description

Background summary

Cystic fibrosis (CF) is an autosomal recessive disease arising from a mutation in the gene coding for the adenosine triphosphate (ATP)-driven chloride ion channel CF Transmembrane Conductance Regulator (CFTR). In the lung, CFTR mutations result in reduced mucociliary clearance, progressive obstructive pulmonary disease, and chronic respiratory infections, which are a major cause of morbidity and mortality in CF patients. Pseudomonas aeruginosa (PsA) is the most prevalent pulmonary pathogen in CF patients. Chronic PsA pulmonary infection is an independent risk factor for accelerated loss of pulmonary function and decreased survival. Chronic PsA infection often results in a mucoid bacterial phenotype and the formation of biofilms that render bacteria refractory to antimicrobial therapy. The eventual acquisition of multi-drug

resistant (MDR) PsA strains and antibiotic resistant PsA biofilms that are difficult to eradicate leaves CF patients with few available treatment options. Over time, chronic lung infections lead to excessive inflammation and bronchiectasis, resulting in either a need for lung transplantation or in death due to respiratory failure.
Lytic bacteriophage therapy offers a novel alternative to antibiotics in the treatment of chronic PsA infections, including those involving MDR strains and biofilm formation. Bacteriophage therapy (BT) has been used for over 100 years, particularly in Eastern Europe, where multiple case reports have demonstrated the safety and tolerability of BT with few adverse events (AEs). However, to date, BT has not been approved as a therapy. Inhalation BT has the advantage of achieving higher drug concentrations at the site of infection without the systemic exposure and AEs of IV or enterally administered therapy. No placebo-controlled, double-blind clinical studies have been conducted to date.

Study objective

Primary Objective:
To evaluate the safety and tolerability of nebulized BX004-A in CF subjects with chronic PsA pulmonary infection.

Exploratory Objective:
To evaluate the effect of BX004-A on sputum PsA burden, lung function, frequency of APEs, and quality of life at various timepoints.

Study design

The clinical development program for BX004-A will be initiated with a Phase 1b/2a randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and tolerability of twice daily inhaled bacteriophages (BX004-A) for up to 10 days. In the Netherlands, subjects are being asked to participate in Part 2 only. This study is descriptive and designed to evaluate the treatment effect of twice daily BX004-A in addition to standard of care inhaled antibiotics in the setting of background CF therapy.
Subjects will receive bacteriophages in addition to their usual inhaled antibiotic regimen so that they receive appropriate antimicrobial coverage according to their usual schedule, and will be included in a 6-month safety follow-up. Final safety assessments will include phone calls 28 days and 6 months after the last dose of study medication to assess adverse events (AEs).
A Data Monitoring Committee (DMC) will monitor safety during both parts of the study. The Sponsor will be unblinded after all subjects complete the Day 28 visit, to allow generation of topline results prior to complete data analysis after the final phone call at 6 months.
The study includes a Screening period followed by a Treatment period. Patients will be enrolled in the study if they are infected with PsA at a minimum density of 10*5 CFU/gram of sputum, and all PsA morphotypes are susceptible to

at least one bacteriophage in BX004-A. Eligible subjects will be randomized (2:1) to receive either twice daily High Dose inhaled BX004-A (minimum n=16) or placebo (minimum n=8) for 10 consecutive days in addition to their usual regimen of inhaled antibiotics. Following 10 days of study drug treatment, all subjects will discontinue either inhaled BX004-A or placebo and continue receiving inhaled antibiotics as per their usual regimen. The standard of care inhaled antibiotic administered daily from Days 1-28 must be the same throughout.

Intervention

Either twice daily High Dose inhaled BX004-A or placebo for 10 consecutive days in addition to the usual regimen of inhaled antibiotics.

Study burden and risks

Lytic bacteriophage therapy offers a novel alternative to antibiotics in the treatment of chronic PsA infections for CF patients.

Possible benefit:
Subject's chronic PsA lung infection may improve from taking part in this study and they may feel better. However, this cannot be guaranteed, especially if they receive placebo (randomization ratio 2:1).

Based on the general understanding of the safety profile of phage, including outcomes of the compassionate phage treatments reported in this indication, it is considered that for cases of chronic PsA pulmonary infections, associated with increased morbidity, the risk of administering nebulized phage that is thoroughly characterized for intrinsic safety and manufactured to meet pre-determined specifications for safety concern parameters, such as endotoxins, exotoxins and sterility, is low.

Burden - Subjects will undergo the following tests/assessments during a period of 6 months, where the largest burden is in the first 28 days:
Venapunction: 2 times;
CFQ-R (Cystic Fibrosis Questionnaire Revised): 3 times;
CFRSD-CRISS (Cystic Fibrosis Respiratory Symptom Diary - Chronic Respiratory Infection Symptom Score: To be completed daily by subject from Day 1 to Day 38;
Physical Examination of the Lungs: 5 times;
Height, weight and BMI: 4 times;
SpO2, blood pressure, respiratory rate, heart rate, and temperature: 5 times;
Collect Sputum (provided spontaneously by coughing or by undergoing sputum induction): 5 times;
For WOCBP urine pregnancy test: 2 times;
Spirometry: 4 times;
To keep daily drug diary: For 10 days.

Possible risks and discomforts from the procedures subjects may experience during the study:
• Blood draws: The risk of blood draws includes discomfort at the site of the blood draw with bruising, bleeding, pain and/or redness at the site of the needle stick, infection, or fainting. Very rarely subjects may get an infection in their blood or a blood clot may form. In very rare cases, the needle might damage a nerve or a blood vessel.
• Sputum induction procedures: If subjects undergo sputum induction, they may experience mild bronchospasm from the medication given to help them cough up sputum.
• Subjects will be asked to complete questionnaires. Some of the questions may make them feel anxious or upset. Subjects does not have to answer any questions that upsets them.

Risks/burden related to study treatment:
BX004-A is administered by inhalation, and it is possible that inhaled BX004-A could cause respiratory side effects and/or bronchospasm soon after inhalation. These include:
• Wheezing,
• Cough,
• Productive cough,
• Rales,
• Dyspnea,
• Acute pulmonary exacerbation,
• Respiratory failure.

Rare risk: Anaphylactic reaction (include hives, itching, tremor, swelling of the face and/or neck, hypotension, difficulty breathing, choking, nausea, vomiting, dizziness, or fainting).

During manufacture of BX004-A, harmful substances made by PsA, like endotoxin and exotoxin, are removed from the final drug product. However, it is always possible that a small amount of bacterial endotoxin or exotoxin escapes the removal process and is present in the vials of bacteriophage that subjects receive.

It is possible that the PsA strains subjects have in their lung become resistant to the bacteriophages in BX004-A and because of this, they may not receive much benefit or clinical improvement from BX004-A.

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

1. Cystic fibrosis patients with chronic Pseudomonas aeruginosa pulmonary infection receiving standard of care CF medications.
2. Age >= 18 years
3. FEV1 >= 40% predicted
4. Clinically stable lung disease
5. Willing and able to provide adequate sputum samples, using any method (spontaneously expectorated, induced, from home or clinic) at designated study visits.

Exclusion criteria

1. Known hypersensitivity to bacteriophages, simethicone, or excipients in the formulation
2. Receipt of prior bacteriophage therapy (BT) within the 6 months prior to Screening
3. Recovery of Burkholderia species from respiratory tract within 1 year prior to screening

4. Currently receiving treatment for allergic bronchopulmonary aspergillosis
5. Currently having treatment for active infection with non-tuberculous mycobacteria
6. History of severe neutropenia
7. History of lung transplant
8. History of solid organ transplant
9. Acquired or primary immunodeficiency syndrome
10. Initiation or change in type of CF modulator therapy less than 3 months prior to screening
11. Pregnant (or planning to become pregnant) or breastfeeding female

Study design

Design

Study phase:	2
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):	19-06-2023
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO

Date:	23-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	01-06-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2022-003810-35-NL
ClinicalTrials.gov	NCT05010577
CCMO	NL83488.000.23