Sputum Pharmacokinetics of a Nebulized Phage Cocktail in Cystic Fibrosis Patients with Chronic *Pseudomonas aeruginosa* Pulmonary Infection: A Phase 1b/2a Randomized, Double-blind, Placebo-Controlled Study

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Disclosures

Urania Rappo:

- Other - Stock options (for employees) - BiomX
- Pharmaceutical Industry Employee (or former employee)- BiomX: all co-authors (except Eitan Kerem)
- Consultant for BiomX: Eitan Kerem

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Background / Introduction

- **Chronic pulmonary infection** with ***Pseudomonas aeruginosa*** (Pa): **increased morbidity** & mortality, and **reduced lung function** in people with **cystic fibrosis** (PwCF)[1,2]
- Most patients **remain infected with Pa** even after treatment with CF transmembrane conductance **(CFTR) modulator** therapy (elexacaftor-tezacaftor-ivacaftor)[3]
- Study Objectives
  - To assess the **safety** and **efficacy** of a phage cocktail (BX004-A) in PwCF with chronic Pa pulmonary infection, including levels of **phage** in **sputum** after start of phage administration

Phage Cocktail

Nebulizer

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1. Cystic Fibrosis Foundation, Executive Summary. https://www.cff.org/medical-professionals/eradication-initial-p-aeruginosa-clinical-care-guidelines#use-of-these-guidelines. 2. Mogayzel PJ, et al. Ann Am Thorac Soc. 2014 Dec; 11(10):1640-50. 3. Nichols DP, et al. J Clin Invest. 2023 May 15;133(10):e167957.

Methods

Ph1b/2a **randomized, double-blind, placebo-controlled, multicenter** study evaluated nebulized BX004-A

- Key Inclusion Criteria
  - Outpatient adult CF subjects
  - Clinically stable lung disease: **FEV_1 (Forced Expiratory Volume in 1 sec) ≥ 40%** predicted
  - **Chronic Pa** infection**: ≥ 1 sputum or throat culture** in past 12 months with Pa (in addition to **Screening sputum** culture)
  - On **chronic inhaled** antibiotics: **tobramycin, aztreonam, or colistin** as standard of care (SOC)
  - Screening **sputum Pa level ≥ 10^5** colony-forming units (CFU/g)
  - All Screening sputum Pa morphotypes **susceptible to at least 1 phage** in BX004-A (3-phage cocktail)
- **Part 1 (n=9)**
  - Randomized (3:1) to BX004-A or placebo **x 7 days**, plus usual inhaled antibiotic
  - Day 1-3: single ascending doses: D1 placebo x1 → D2 low dose x 1 → D3 high dose x1
  - Day 4-7: twice daily high dose x 4 days
- **Part 2 (n=34)**
  - Randomized (2:1) to twice daily BX004-A or placebo x 10 days, plus usual inhaled antibiotic
  - Day 1-10: **twice daily** high dose x **10 days**

Results / Conclusion

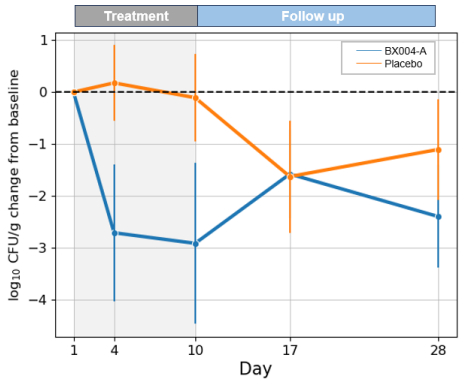
Part 1 (n=9); BX004-A: n=7; placebo: n=2

- Mean sputum Pa change from baseline at D15: **-1.42 log** CFU/g (BX004-A) vs. **-0.28 log** CFU/g (placebo)
- **Phages detected in sputum** of **all subjects** treated with BX004-A in ≥ 1 timepoint during treatment, including in 2 subjects 1 week after end of treatment (EOT)

Part 2 (n=34); BX004-A: n=23; placebo: n=11

- In subjects with quantitative sputum Pa CFU at baseline, **3/21 (14.3%) on BX004-A** had a **negative Pa sputum culture at D10 (EOT)**, vs **0/10 (0%) on placebo**
- **During treatment: no adverse events of special interest** or **serious adverse events**

Figure 1. Mean **change from baseline** of sputum Pa in subjects on **continuous** inhaled antibiotics (rather than cycling/ alternating regimens). Mean **sputum Pa CFU reduction** at **D10: -2.91 log** CFU/g (BX004-A, n=7) vs **-0.10 log** CFU/g (placebo, n=5)



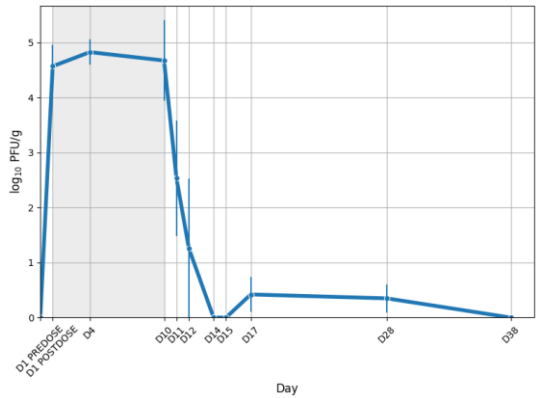
Shaded area: treatment period (D1-D10); Error bars: Standard error

Table. Number of subjects with **phage detected in sputum**, by timepoint

Visit	BX004-A (N=23)	Placebo (N=11)
Day 1 pre-dose (Baseline)	0/22 (0%)	0/10 (0%)
Day 1 post-dose (3h)§	16/17 (94%)	0/9 (0%)
Day 4	22/22 (100%)	0/10 (0%)
Day 10*	12/19 (63%)	0/9 (0%)
Day 17	2/22 (9%)	1/11 (9%)Δ
Day 28	2/22 (9%)	0/11 (0%)
Day 38†	0/12 (0%)	0/6 (0%)

Shaded area: treatment period (D1-D10). §D1 post-dose sample: optional. *Sputum samples at D10 were collected between D10-D13, per protocol visit window. ΔOutlier; may be due to resident phage (ongoing analysis). †D38 sputum collection was added after protocol amendment and available in subset of subjects

Figure 2. Mean **phage levels** (log PFU/g) in sputum of **BX004-A treated** subjects



Shaded area: treatment period (D1-D10); Error bars: Standard error.
PFU/g: plaque-forming units/g

PK analysis of **phage cocktail** in **sputum** detected **phage** in ≥ 1 **timepoint** for **all subjects** treated with phage, including in 2 subjects 1 week after EOT (D17) and 2 subjects at D28

Conclusion: BX004-A showed **favorable safety** and notable **microbiologic efficacy** with **detectable phage** in the **sputum** of all subjects during phage therapy

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