Safety and efficacy 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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CONFLICT OF INTEREST(S):

- E Kerem is a consultant for BiomX
- Other co-authors are current or former employees of BiomX and may own company securities
BACKGROUND

- *Pseudomonas aeruginosa* (Pa): associated with pulmonary exacerbations in people with cystic fibrosis (PwCF) even in the era of elexacaftor/tezacaftor/ivacaftor (ETI)

- **Bacteriophage (phage) therapy**: novel *alternative or adjunct* to antibiotics

- **Phase 1b/2a clinical trial of nebulized phage cocktail (BX004-A) in pwCF with chronic Pa pulmonary infection**
  - **Primary objective**: safety & tolerability of BX004-A
  - **Exploratory objectives**: efficacy of BX004-A on sputum Pa burden and clinical outcomes
METHODS

Ph1b/2a Randomized Clinical Trial of Nebulized Phage for *Pseudomonas aeruginosa* Pulmonary Infection

- Outpatient adult CF subjects (total n=43)

**Key Inclusion Criteria**

- Clinically stable lung disease: **Forced Expiratory Volume in 1 sec (FEV1) ≥ 40% predicted**
- **Chronic Pa pulmonary infection**: ≥ 1 sputum or throat culture in past 12 months positive for Pa (in addition to Screening sputum culture)
- On chronic inhaled antibiotics (*tobramycin, aztreonam, or colistin*) as standard of care (SOC)
- Screening sputum Pa level ≥ 10⁵ colony-forming unit (CFU/g)
- All Screening Pa morphotypes **susceptible to ≥ 1 phage** in BX004-A

**Part 1 (n=9):** randomized (3:1) to BX004-A or placebo x7 days, plus usual inhaled antibiotic

- D1-3: single ascending doses (D1 placebo x1 → D2 low dose x1 → D3 high dose x1)
- D4-7: twice daily high dose x 4 days

**Part 2 (n=34):** randomized (2:1) to twice daily BX004-A or placebo x10 days, plus usual inhaled antibiotic

- D1-10: twice daily high dose x 10 days
PART 1: STUDY DESIGN

Randomized (3:1) to single-ascending dose and multiple doses

<table>
<thead>
<tr>
<th>Part 1 (single-ascending and multiple dose portion, n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (3:1) to BX004-A or placebo x 7 days, on top of standard of care</td>
</tr>
</tbody>
</table>

- n=7 nebulized BX004-A phage therapy
- n=2 nebulized placebo
- Treatment duration: 7 days (3 single ascending dosing days, 4 multiple dosing days)
PART 1: RESULTS

Part 1 (n=9)
- Mean sputum Pa colony forming unit (CFU/g) change from baseline at D15 was \(-1.42 \log (BX004-A, n=7)\) vs. \(-0.28 \log \) (placebo, n=2)

<table>
<thead>
<tr>
<th>BX004-A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>7</td>
</tr>
<tr>
<td>Mean Pa CFU Reduction at D15 (range)</td>
<td>(-1.42 \log_{10} (-3.27 to -0.37))</td>
</tr>
</tbody>
</table>
PART 2: STUDY DESIGN

Randomized (2:1) to twice daily BX004-A or placebo x 10d, on top of standard of care

- **Larger sample size** than Part 1 (n=23 on BX004-A, n=11 on placebo)
- **Longer duration** of therapy (10 days), high dose twice daily
- **Later in-clinic follow-up** to at least Day 28 (18 days after last dose)
**Inhaled antibiotic regimens in CF**

- **Continuous**: same inhaled antibiotic before, during, and after study drug
- **Alternating**: inhaled antibiotic A x 28 days, alternating with inhaled antibiotic B x 28 days
- **Cycling**: off-cycle with no inhaled antibiotic x 28 days then on-cycle x 28 days
- **Study drug** on Day 1 started with on-cycle (if on cycling antibiotic) or next alternating antibiotic (if on alternating regimen)

**PART 2: STUDY DESIGN**

Timing of study drug with SOC chronic inhaled antibiotics
### PART 2 (n=34): **KEY BASELINE CHARACTERISTICS** (Safety Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BX004-A (N=23)</th>
<th>Placebo (N=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years (SD)</td>
<td>36.8 (12.06)</td>
<td>33.1 (8.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (60.9)</td>
<td>5 (45.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>EU (Spain, Netherlands, Czech Republic), n (%)</td>
<td>11 (47.9)</td>
<td>6 (54.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>US, n (%)</td>
<td>7 (30.4)</td>
<td>3 (27.3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Israel, n (%)</td>
<td>5 (21.7)</td>
<td>2 (18.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>CFTR modulators, n (%)</td>
<td>17 (73.9)</td>
<td>9 (81.8)</td>
<td>0.94</td>
</tr>
<tr>
<td>Inhaled antibiotic (during study drug)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin, n (%)</td>
<td>12 (52.2)</td>
<td>5 (45.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Tobramycin, n (%)</td>
<td>8 (34.8)</td>
<td>4 (36.4)</td>
<td>0.92</td>
</tr>
<tr>
<td>Aztreonam, n (%)</td>
<td>3 (13)</td>
<td>2 (18.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Type of inhaled antibiotic regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous, n (%)</td>
<td>9 (39.1)</td>
<td>6 (54.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cycling, n (%)</td>
<td>8 (34.8)</td>
<td>3 (27.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Alternating, n (%)</td>
<td>6 (26.1)</td>
<td>2 (18.2)</td>
<td>0.61</td>
</tr>
<tr>
<td>% Predicted FEV1: mean (SD), n</td>
<td>63.8 (21.07), 22</td>
<td>59.0 (17.48), 11</td>
<td>0.52</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> log₁₀ CFU/g in sputum on D1; mean (SD), n*</td>
<td>6.65 (1.39), 21</td>
<td>6.8 (1.5), 10</td>
<td>0.35</td>
</tr>
<tr>
<td>Range</td>
<td>3.38-8.13</td>
<td>3.34-8.04</td>
<td></td>
</tr>
</tbody>
</table>

*modified intent-to-treat population; SD: standard deviation; CFTR: CF transmembrane conductance regulator*
**PART 2: RESULTS**

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** (end of treatment), with prior duration of chronic Pa 13-35 years, vs 0/10 (0%) on placebo

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of Pa infection (years)</th>
<th>Baseline Pa in sputum (CFU/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>$2.40 \times 10^3$</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>$5.60 \times 10^7$</td>
</tr>
<tr>
<td>3*</td>
<td>35</td>
<td>$1.09 \times 10^7$</td>
</tr>
</tbody>
</table>

*Subject had negative sputum culture for *P. aeruginosa* at D4, D10, D28, D38, D63, D151 and at most recent standard of care clinic visit D167
PART 2: RESULTS (cont’d)

In subjects on **continuous** inhaled antibiotics (rather than cycling / alternating regimens)

- Mean **sputum Pa CFU reduction at D10**: -2.91 log (BX004-A, n=7) vs -0.10 log (placebo, n=5), **Figure 1**

* Figure 1: Mean (SE) sputum Pa CFU/g log change from baseline in subjects on **continuous** inhaled antibiotics

* $p=0.16$
In subjects on **continuous** inhaled antibiotics and on **ETI**

- Mean sputum Pa CFU reduction at D10 -4.82 log (BX004-A, n=5) vs -0.11 log (placebo, n=5) (p<0.05), **Figure 2**

**Figure 2**: Mean (SE) sputum Pa CFU/g log change from baseline in subjects on **continuous** inhaled antibiotics and on **ETI**

* p=0.02
PART 2: RESULTS (cont’d)

In subjects on **continuous** inhaled antibiotics, on **ETI** and with **FEV<sub>1</sub> <70%**

- Mean sputum Pa CFU reduction at D10: \(-3.84 \text{ log} \) (BX004-A, n=4) vs \(-1.03 \text{ log} \) (placebo, n=3), Figure 3
- Relative **FEV<sub>1</sub>** improvement of **+8.89%** at D17 between groups (change from baseline +5.66% in BX004-A vs -3.23% in placebo), Figure 4 (BX004-A, n=4; placebo, n =4)

![Figure 3](image1.png)

**Figure 3:** Mean (SE) sputum Pa CFU/g log change from baseline in subjects on **continuous** inhaled antibiotics, on **ETI** and with **FEV<sub>1</sub> <70%**

* \( p=0.22 \)

![Figure 4](image2.png)

**Figure 4:** Relative FEV1 improvement in subjects on **continuous** inhaled antibiotics, on **ETI** and with **FEV<sub>1</sub> <70%**

* \( p=0.22 \)

**During treatment,** there were **no adverse events of special interest or serious adverse events** (in both Parts)
CONCLUSION

Phase 1b/2a clinical trial assessed safety, tolerability, and efficacy of BX004-A in CF subjects with chronic *P. aeruginosa* pulmonary infection:

BX004-A showed **favorable safety** and **notable microbiologic and clinical efficacy**

Next steps

**Phase 2b clinical trial planned**
- Randomized, double-blind, placebo-controlled, multi-center study in approximately 60 patients with CF and chronic *P. aeruginosa* pulmonary infection
- Randomized 2:1 to BX004 or placebo as twice daily inhalation x 8 weeks
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