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Chronic *Pseudomonas aeruginosa* pulmonary infection treated with a nebulized phage cocktail in patients with cystic fibrosis: a phase 1b/2a randomized, double-blind, placebo-controlled, multicenter study

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BACKGROUND

- ***Pseudomonas aeruginosa*** (PsA): causes **pulmonary** infections and repeat **exacerbations** in **cystic fibrosis** (CF) patients
- **Bacteriophage (phage) therapy:** novel **alternative or adjunct** to antibiotics

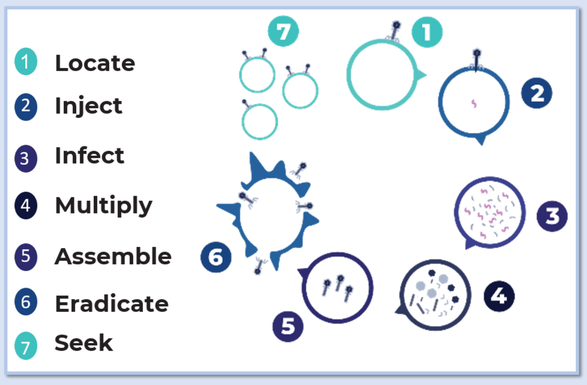
Phase 1b/2a randomized, double-blind, placebo-controlled, multicentre study of **nebulized phage cocktail** (BX004-A) in CF subjects with **chronic PsA pulmonary infection**

- **Primary objective**: safety & tolerability of BX004-A
- **Exploratory objectives**: effect of BX004-A on sputum PsA burden, pharmacokinetics (PK) of BX004-A in sputum, and clinical outcomes

METHODS

- **Outpatient adult CF subjects** (total n=43)
- Key **Inclusion** Criteria
  - Clinically stable lung disease: **Forced Expiratory Volume in 1 sec (FEV1) ≥ 40% predicted**
  - **Chronic PsA pulmonary infection**: ≥ 1 sputum or throat culture in past 12 months positive for PsA (in addition to Screening sputum culture)
  - On **chronic inhaled** antibiotics (**tobramycin, aztreonam, or colistin**) as standard of care (SOC)
  - Screening **sputum PsA level ≥ 10^5** colony-forming unit (CFU/g)
  - All Screening PsA morphotypes **susceptible to ≥ 1 phage** in BX004-A
- **Part 1, n=9 (single-ascending and multiple dose portion):** randomized (3:1) to BX004-A or placebo x 7 days, plus usual inhaled antibiotic (D1-7)
- **Part 2, n=34 (multiple dose portion):** randomized (2:1) to twice daily BX004-A or placebo x 10 days, plus usual inhaled antibiotic (D1-28)
- Safety **follow-up until 6 months** after last dose

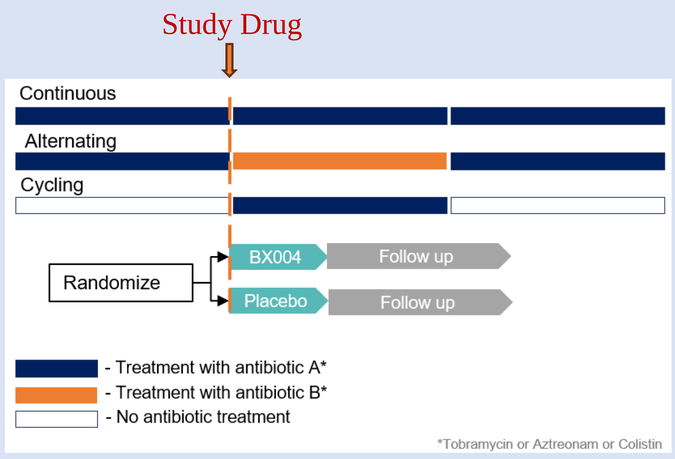
Phages: self-amplifying therapeutic agents



3-phage cocktail

Nebulizer

Part 2 Study Design: timing of study drug with SOC chronic inhaled antibiotic



Inhaled antibiotic regimens in CF

Continuous: **same** inhaled antibiotic before, during, and after study drug

Alternating: inhaled antibiotic A x 28d, **alternating** with inhaled antibiotic B x 28d

Cycling: **off-cycle** with no inhaled antibiotic x 28d then **on-cycle** x 28d

- **Study drug** on D1 started with **on-cycle** (if on cycling antibiotic) or next **alternating antibiotic** (if on alternating regimen)

RESULTS

Part 1 (n=9): Topline results after **D15 visit**
- Randomized to **BX004-A: n=7**; **placebo: n=2**
- Mean **sputum PsA reduction** at D15 (vs baseline): **-1.42 log** CFU/g (BX004-A) vs. **-0.28 log** CFU/g (placebo)

Part 2 (n=34): Key Baseline Characteristics (Safety Population)

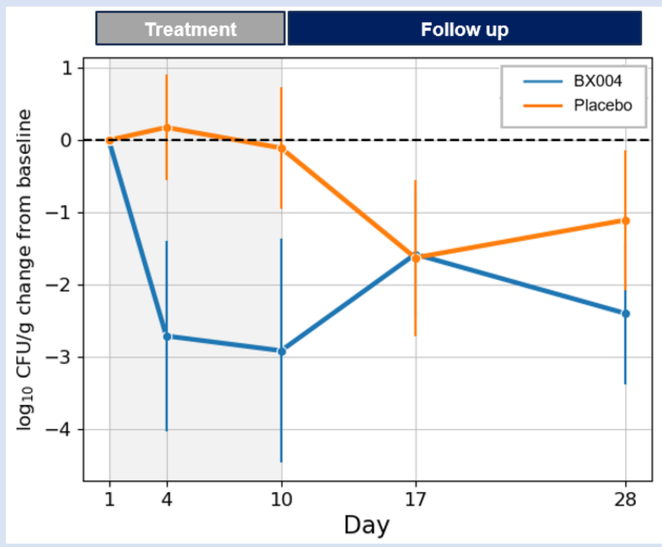
Characteristic	BX004-A (N=23)	Placebo (N=11)
Age, mean, years (SD)	36.8 (12.06)	33.1 (8.9)
Male, n (%)	14 (60.9)	5 (45.5)
EU (Spain, Netherlands, Czech Republic), n (%) US, n (%) Israel, n (%)	11 (47.9) 7 (30.4) 5 (21.7)	6 (54.5) 3 (27.3) 2 (18.2)
CFTR modulators, n (%)	17 (73.9)	9 (81.8)
Inhaled antibiotic (during study drug) Colistin, n (%) Tobramycin, n (%) Aztreonam, n (%)	 12 (52.2) 8 (34.8) 3 (13)	 5 (45.5) 4 (36.4) 2 (18.2)
Type of inhaled antibiotic regimen Continuous, n (%) Cycling, n (%) Alternating, n (%)	 9 (39.1) 8 (34.8) 6 (26.1)	 6 (54.5) 3 (27.3) 2 (18.2)
% Predicted FEV1: mean (SD), n	63.8 (21.07), 22	59.0 (17.48), 11
P. aeruginosa $\log_{10}$ CFU/g in sputum on D1; mean (SD), n* Range	6.65 (1.39), 21 3.38-8.13	6.8 (1.5), 10 3.34-8.04

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

RESULTS (Cont'd)

Part 2 (n=34): Topline results after **D28 visit**
- Randomized to **BX004-A: n=23**; **placebo: n=11**
- In subjects with quantitative sputum PsA CFU at baseline: **3/21 (14.3%)** on **BX004-A** had sputum **culture negative for PsA at D10** (end of treatment [EOT]), vs **0/10 (0%) on placebo**
- In a prespecified subgroup on **continuous inhaled antibiotics** (rather than cycling or alternating regimens), mean **sputum PsA CFU reduction** at D10 (EOT): **-2.91 log** (BX004-A, n=7) vs **-0.10 log** (placebo, n=5), **Figure 1**.

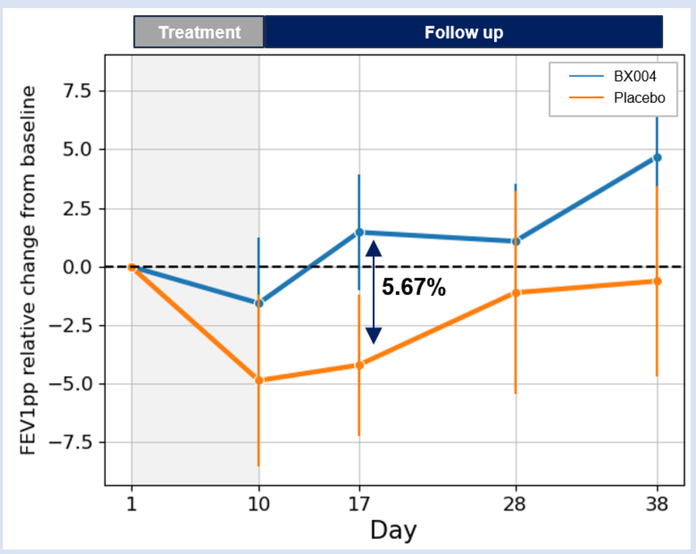
Figure 1: Mean (SE) sputum PsA CFU/g log change from baseline in subjects on continuous inhaled antibiotics



SE: standard error

- **BX004-A** showed a positive clinical effect in lung function **with relative FEV1** improvement of **+5.67% at D17 vs placebo** (change from baseline +1.46% vs -4.21%) in subjects with reduced lung function (**FEV1 <70%:** BX004-A n=12; placebo n=8), **Figure 2**.

Figure 2: Mean (SE) % predicted FEV1 relative change from baseline in subjects with reduced lung function (% predicted FEV1 <70%)



SE: standard error

Both Parts
- Study drug **well-tolerated**; no treatment-related serious adverse events
- **No premature discontinuations** from study drug or study
- **No emerging treatment-related resistance** to BX004-A in treated subjects
- PK of BX004-A: **phage** detected **in sputum** of **all BX004-A** subjects **during treatment**, including in several subjects after EOT at Day 15 (Part 1) and Day 17 & 28 (Part 2)

CONCLUSION

- Study drug **well-tolerated** in **Phase 1b/2a clinical trial** assessing nebulized phage BX004-A in CF subjects with chronic PsA pulmonary infection
- Notable **microbiologic and clinical efficacy** in BX004-A treated subjects

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DISCLOSURES

UR, AC, IM, EKa, JG, HN, IL, TC, IW, HS, IV, JJ, RM, TA, OB, NB, VL, YT, YZ, MG, RV, and MB are current or former employees of BiomX and may own stock; EKe. is a consultant for BiomX