# Prevention of exacerbations/management of CF patients chronically infected with *Pseudomonas aeruginosa*

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Development of Inhaled Antibacterial Treatments for Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis
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# Hypothetical Proposed Development Plan

- Sponsor “A” is proposing to use a novel inhaled antipseudomonal drug “X” to prevent exacerbations or manage patients with cystic fibrosis who are chronically infected with *P. aeruginosa*
- Population: pediatric, adolescents, adults
- Study design: inhaled study drug “X” vs. “standard of care” inhalational antibacterial therapy (for example: tobramycin or aztreonam)

# Key Protocol Considerations

- Potential Efficacy Endpoints:
  - Changes in percent predicted FEV1 from baseline
  - Changes in patient-reported outcomes (CFRSD-CRISS or CFQR) scores from baseline
  - Combination of the above? Other endpoints:
  - Frequency/severity of exacerbations, prolongation of interval between exacerbations?
- Proposed Efficacy evaluation: superiority vs. non-inferiority of study drug “X” vs. standard of care
- Study Population: selecting for high-risk based on age, treatment experience, baseline FEV1 and microbiology. Homogeneous population will allow for better interpretation of results.
- Duration of trial(s) and dosing schedule to assess primary endpoint: multiple cycles or continuous daily use for $\geq$6 months? $\geq$1 year?

# Issues to Consider

- No endpoints validated with long term outcomes, although ppFEV1 is clinically meaningful
- Rates of exacerbation vary by age
- No established definition of exacerbation, and may vary by age group
- No data on effectiveness of standard of care, of dynamic nature
- Non-inferiority vs. superiority hypotheses: difficulty establishing an NI margin
- CFRSD-CRISS scores validated only in adults and children older than 12 year of age

# Panel Questions

1. What is/are clinically meaningful objective(s) for the trials?

   - Lung function preservation, improvement of symptoms, decrease severity of exacerbations, a combination of these? Other benefits?

2. What selection criteria would best target the study population most likely to demonstrate a treatment benefit?
3. What is the optimal primary endpoint and how long should patients be followed?
4. How should we monitor potential risks (resistance, co-infections, emergent pathogens)?


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# Back-up Slides

**TOBI® PODHALER™** (tobramycin inhalation powder), for oral inhalation use

Initial U.S. Approval: 1975

----------INDICATIONS AND USAGE----------

TOBI Podhaler is an antibacterial aminoglycoside indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa.*

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV1) <25% or >80%, or patients colonized with *Burkholderia cepacia*

**CAYSTON®** (aztreonam for inhalation solution)

Initial U.S. Approval: 1986

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CAYSTON and other antibacterial drugs, CAYSTON should be used only to treat patients with cystic fibrosis (CF) known to have *Pseudomonas aeruginosa* in the lungs.

----------INDICATIONS AND USAGE----------

CAYSTON is a monobactam antibacterial indicated to improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*. Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV1<25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.