Overview and Issues: Developing Inhalational Products for the Treatment of Chronic MRSA Infection in Cystic Fibrosis

Shrimant Mishra, MD, MPH
Medical Officer
Division of Anti-Infective Products, FDA

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State of Problem

- Increasing prevalence of *Staph. aureus* infection, both MSSA and MRSA
  - Change in type of MRSA over time (SCC mec type)
  - Biofilm development; Small Colony Variants (SCV)
    - More difficult to treat
  - Higher rates in 10-30 year olds
  - Declines in pulmonary function and increases in mortality; less return to baseline post exacerbation
  - No approved therapy and no standardized therapy to treat
    - Oral therapy (TMP-SMX, rifampin), nebulized vancomycin, combination

Targeted Inhaled Therapy

- Benefit
  - Act locally with less systemic exposure
  - May use drug with known safety properties

However, may add to inhaled therapy burden of CF patients.

Trial Design Considerations

- Placebo controlled vs Active controlled
  - Issues with ethics, feasibility and limits on duration of placebo trial but superiority could be more easily demonstrated; only opportunity before becomes standard of care; provide definitive evidence of the benefits of treatment
  - Issues with choosing appropriate comparator and ability to demonstrate superiority/establish non-inferiority margin in active controlled trial but may be easier to do the trial and for longer
- Duration/mode of therapy
  - Cyclical therapy used commonly in other CF infections but should 28 day on/off paradigm be followed or should shorter cycles or continuous therapy be considered?
- Enrich population
  - Can target subjects depending on endpoint used but may limit generalizability

Potential Endpoints

- Clinical (Exacerbations, time to hospitalizations)
  - Issues: How to define, what is study duration to capture adequate number of events, do you need long term data (mortality)?
- Microbiologic (Eradication/reduction of pathogen from sputum)
  - Issues: Are there standardized sampling/culture methods, can we correlate with clinical improvement (short and long term), is eradication possible and if not what would be definition of reduction?
- Biomarkers/Surrogates (FEV1% predicted)
  - Issues: What is a clinically relevant change, can we correlate with clinical improvement (short and long term)?
- PROs (CFR-RSD, CFQ-R)
  - Issues: Are validated PROs available, What is a clinically relevant change, can it stand alone as a primary endpoint if not supported by microbiologic or pulmonary function changes?

Quick Thoughts

- Not all issues can be addressed
- Questions for Consideration
  - What is of most value to this particular patient population
    - What is their risk threshold, kinds of data requested
    - Need for standardization and consolidation?
  - How do we ensure an adequate safety database?
  - What are biggest barriers for investigators?
  - How to leverage registries/clinical consortiums