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

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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