Case Study on Developing an Inhalational Therapy for Non-Cystic Fibrosis Bronchiectasis

Part 1: Patient Selection and Trial Duration

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Developing an Inhaled Antibacterial for NCFB Patients

• Company A wants to develop Drug Y to reduce the incidence of exacerbations due to bacterial pathogens in patients with NCFB

• They are trying to identify a patient population that is most likely to demonstrate a treatment benefit in their trials
Issues

• No antibacterial drugs are currently approved to reduce the incidence of exacerbations due to bacterial pathogens in patients with NCFB
  – Previous trials of inhaled antibacterial drugs in NCFB patients have failed to demonstrate benefit over the current standard of care

• Uncertainties regarding an appropriate trial design
Selecting the Study Population

• NCFB patients are a heterogeneous population
  – Different etiologies for NCFB
  – Severity of illness and co-morbid conditions vary
  – Incidence of exacerbations may vary by:
    • individual patient
    • over time
    • season
    • region
Additional Factors

– A variety of micro-organisms may cause exacerbations, not just bacteria
  • How to deal with the following:
    – History of nontuberculous mycobacteria pulmonary infection or allergic bronchopulmonary aspergillosis

– Patients are on concomitant adjunctive therapies, some may require maintenance systemic corticosteroids
How to select a population most likely to show treatment benefit?

• History of multiple exacerbations in the prior year?
  – Patients enrolled in previous trials tended to have fewer exacerbations during the trials than in the prior year
  – Only include patients who required hospitalization during prior exacerbations?
  – What criteria should be used to define a prior exacerbation?
• Concomitant use of macrolide therapy?
• Only include patients with multi-lobar involvement?
• Other demographic or disease-related factors?
• What patient characteristics or co-morbidities would lead to trial exclusion?
Duration of Phase 3 Trials

• Prior Phase 3 trials lasting 1 year may not have been long enough to adequately assess whether a new study therapy reduces the frequency of exacerbations to a clinically meaningful extent and whether such an effect would be durable beyond a year

• Practical considerations of conducting trials longer than 1 year
  – Cost
  – May not be ethical for patients to stay on placebo for a period of two or more years
Trial Duration Considerations (cont’d)

• Another option could be to consider a study which includes an open-label extension period to address ethical issues relating to the extended use of placebo.
• However, such a design would not be as informative as a randomized trial with a two year evaluation period.
• Longer trials could also assess for additional safety issues with chronic use and development of bacterial resistance.
Panel Questions

1. How would you advise Company A to enrich their trials for subjects most likely to demonstrate a treatment benefit?

2. What is an appropriate duration for the Phase 3 trials?