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?


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