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

Part 2: Endpoint Considerations

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Trial Design and Endpoint

- Trial Design: Superiority
  - NI trial not an option given lack of established treatments
- A key goal in management is reduction of PEs
  - Major driver of future complications: ↑ healthcare costs, ↓ quality of life, significant morbidity
  - Trial Objective: Reduction in exacerbations, reduction in hospitalizations, decreased time on IV antibacterials, etc.
- Chronic use → Need for rigorous evaluation of treatment over a sufficient length of time

Time to First Exacerbation (TFE)

- Relatively parsimonious endpoint and easy to analyze
- Ignores all clinical events occurring after initial PE
- Easily misinterpreted, *e.g. a delay in the initial exacerbation followed by more severe exacerbations*
- Inconsistent results from prior development programs
  - No evidence TFE predicts long term clinical outcome
  - Less clinically relevant for patients expected to be on therapy for prolonged periods or life-long

Potential Clinical Endpoints for Future Clinical Trials in NCFB

- Total (first and recurrent) pulmonary exacerbations during the trial
- Clinical severity of exacerbations, as measured by:
  - Duration of exacerbation,
  - Duration of hospitalization for exacerbation episode,
  - Days of intravenous antibacterial therapy
- Co-primary endpoint
  - Total exacerbations & severity of exacerbations

Frequency of Exacerbations: Some Considerations

- In some cases, PEs are less frequent, but severe and prolonged
- A limitation is in assessing patient “at risk” time
  - While experiencing an exacerbation patients are not at risk for a subsequent exacerbation
    - This may unduly benefit the treatment arm with patients having longer, more severe exacerbations
  - Investigators may have varying opinions of when an exacerbation has ended and severity

Frequency of Exacerbations: Analytical Considerations

- Analysis of total exacerbations as a count

- Strengths: Captures all exacerbations, can adjust other variables in the model, generates an estimate of the mean

- Weaknesses: Ignores correlation among multiple events, fails to account for ‘at-risk’ time, does not capture duration/time of exacerbations

Counting Approach for Total Exacerbations

Recurrent time-to-event approach: Modified Cox PH model-generates est. of the risk of recurrent events

- Andersen and Gill [1]
  - Analyzes time between events (gap time) independently
  - Time-varying covariates to account for correlations and clustering on patient
  - Events assumed to be of the same nature/type and assumes proportionality
  - *Application: Focus is on overall effect on the intensity of occurrence of recurrent event*
- Prentice, Williams and Peterson [2]
  - Analyzes gap times using conditional risk sets (condition based on prior event(s))
  - No baseline hazard assumption
  - *Application: When the occurrence of the 1st event increases likelihood of a re-occurrent, i.e. risk of a future PE impacted by prior event*

1. Andersen & Gill, Ann Stat 1982;10:1100-20.; 2. Prentice, Williams & Peterson, Biometrika 1981; 68:373-79.

Co-Primary Endpoint

- Incorporates two important clinical endpoints
  - Total PEs over the course of the trial and severity of exacerbations
- Need to power trial on both endpoints
  - ~ prev. 139 per 100,000 ≥ 18 yrs, increases with age [1]
  - ~ 9% annual ↑ in prevalence [2] (in persons ≥65 yrs.)
  - Highly heterogeneous patient population

1. Weycker, Chr Resp Dis 2017; 14(4) 377-384. ; 2. Seitz, Chest 2012; 142:432-439.

Other Endpoints

Quality of Life Measures

- AIR-BX1 and AIR-BX2: Adj. mean change from BL in QOL-B-RSS at Week 4
  - AIR-BX1: 0.8 (95% CI: -3.1, 4.7), p=0.68
  - AIR-BX2: 4.6 (95% CI: 1.1, 8.2), p=0.011 (authors concluded no clinical significance)
  - ORBIT and RESPIRE: QoL-B at Week 48: No statistically significant findings
  - RESPIRE trials: SGRQ symptoms domains: Inconsistent results

Pulmonary function

  - No differences observed in ORBIT or RESPIRE trials
  - Varying results across prior clinical trials

- Measure sensitivity associated with disease severity of trial population

Panel Discussion

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?
3. Discuss the importance of the non-TFE endpoints.
4. Is a co-primary endpoint of total exacerbations and severity of exacerbations clinically meaningful?
5. What other endpoints should be considered?


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