Trial Design, Endpoints for Disease Modifying Drugs in Parkinson’s Disease

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The views expressed in this presentation do not necessarily reflect any position of the Food and Drug Administration
Impetus

- Drugs to slow the progression of diseases such as Parkinson’s, Alzheimer’s are under development.

- Innovative trial designs/endpoints/analyses with model based statistical methodologies being proposed to discern ‘protective drug effect’.

- FDA is asked to comment on the acceptability of these trial designs and pre-specified analyses.
  - Critical to understand disease/baseline characteristics, disease progression, placebo/drug effects, and statistical issues (Missing data, etc).
Key Scientific Questions

1. What are the influential demographic factors influencing the baseline clinical scores (UPDRS) and progression?
2. How do we describe the progression of Parkinson’s disease (Linear/Nonlinear)?
3. Why patients drop-out of these trials?
4. What is the impact of missing data on hypothesis testing for discerning symptomatic vs protective benefits?

Unified Parkinson Disease Rating Scale (UPDRS)
The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. 199 represents the worst (total) disability, 0--no disability.
To understand issues with delayed start design

1. IDENTIFY KEY QUESTION(S)
   Build Disease & Drug Model
   MECHANISM-SYMPTOMS-OUTCOMES
   TIME

2. Extract Clinical Trial Information*
   - PATIENT DEMOGRAPHICS
   - DESIGN
   - PLACEBO/DRUG EFFECTS
   - DROP OUT PATTERN

3. Simulate Scenarios
   - TRIAL DESIGN
   - SAMPLE SIZE
   - SAMPLING TIMES
   - ENDPOINTS, ANALYSIS

4. Plug Sponsor Data, Play & Decide
   (Go/No Go, trial design)

UPDATE
Future Work

• We are summarizing all our findings on disease progression characteristics, drop-out, appropriate primary endpoint and hypothesis testing methodology.
• We are testing protocol amendments using the simulation codes that are developed to understand prospectively what the sponsor and FDA can expect.
• We will discuss our updated findings at upcoming Clinical/Statistics joint meeting being planned for 2007.
Project Timelines

Advisory Committee Meeting (Clinical/Statistical)

External/Internal presentations
  • CPSC
  • DIA

ACCP Symposium

Data Collection

Concept Framework

Jan, 2005

Sep, 2005

Sep 2005

Oct 06
Jan 07...

07
Summary of discussions

• Disease models are useful
• Recommendation for sharing the detailed model, diagnostics etc. at a future meeting
• Duration of the active phase vs. placebo phase (36 weeks each) based on current data (may be different as we gather more data)
• How do you manage need for rescue medication in a study (add-on design, comparison to placebo, drop out of the study etc.)
• EOP2a type of meetings very helpful in this context to discuss study designs
• For a neuroprotective drug, length of the trial needs to be longer...so concern re: ability to have sufficient data early such as for an EOP2a meeting.....we need better tools (e.g. biomarkers) to figure this effect early.
• Should the study be done in early or advanced Parkinson’s disease for neuroprotective effects? (given that this is a slow progressing disease, earlier the better)
• What if the sponsor’s disease progression model differs from the FDAs? FDA open to evaluate sponsor’s proposal, just like any other IND/NDA review
• Prior data available on disease models indicates lot of consistency
• Could background medication affect the placebo model?
• While delayed start design is presented here, this study design is not mandatory
• Dose response recommended (at least 2 doses in these neuroprotection studies)...should this be fixed dose parallel, and or within subject dose response?
• Problems of this type can only be solved with multi-disciplinary collaboration – absolutely necessary
Thank You

http://www.fda.gov/ohrms/dockets/AC/06/Slides