Regulatory Workshop on Clinical Trial Designs in Neuromyelitis Optica and Spectrum Disorders United States Perspective

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent Food and Drug Administration's (FDA's) views or policies.

- The speaker has no financial interest or other relationship with the manufacturer of any commercial product discussed or with the manufacturer of any competing commercial product.

New Drug Application (NDA) or Biologic License Application (BLA)

Reports of adequate and well-controlled investigations are needed to determine whether there is substantial evidence to support any claims of effectiveness

Elements of adequate and well controlled studies

- Clear statement of the objectives
- Design that permits a valid comparison with a control to provide a quantitative assessment
- Assurance that patients have the condition
- Assignment between groups minimizes bias
- Minimize bias of subjects, observers and analysts
- Well defined and reliable method of assessment
- Analysis of the results

Study Design/Control

- Superiority compared to control

  (any of the following)

  – Can be superiority to current standard of care
  – Can be superiority as an “add on” to another therapy
  – Can be superiority to no treatment

Assignment between groups minimizes bias

- Randomize between treatment arms

Acceptable Endpoints

- Measurement of visual function
- Improvement or Prevention of Loss
- Equivalent to doubling/halving of visual angle
  - High contrast visual acuity - 3 line change
  - Low contrast visual acuity - 3 line change
  - Visual Field
  - Color vision

Endpoints which need more work

- Nerve fiber layer
  - Preventing the absence of the nerve fiber layer could be an acceptable endpoint
  - In the presence of a nerve fiber layer, decreases do not have clear clinical meaning

Endpoints of Questionable Value

- Relapse of Optic Neuritis
  - It is unlikely to make a difference to a patient whether the visual loss comes from a sustained loss or multiple acute losses
    - For example, it is better to have 4 episodes which result in 20/40 (0.3 logMAR) vision than to have 2 episodes which result in 20/80 (0.6 logMAR) vision

Timepoints

- Time is needed to demonstrate that treatment changes the natural history

- One year or greater timepoint recommended due to known potential for optic neuritis to improve with time

Minimize Bias

- Masking
  - Patients
  - Investigators
  - Analysts
- Ancillary treatments and timing of study visits should be the same for all groups

Analyses

- Evaluation of the likelihood that any findings are due to chance
  - Two sided confidence interval
  - $p < 0.05$
  - Adjustments for multiplicity and for interim looks at the data

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