Regulatory Perspective on Endpoints and Therapeutic Development

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- 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.

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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

Minimize Bias

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

Study Design/Control

- In the absence of any established or approved therapy:
  - Superiority compared to concurrent control group

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

Functional 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

Anatomic Endpoints

- Preservation of the structures needed for visual function
  - i.e., Prevention of the loss of photoreceptors
- CMV Retinitis Precedent
  - Preservation of intact photoreceptor border

Evaluation of Lesion Border

- Optical Coherence Tomography (OCT)
- Fluorescein Auto Fluorescence (FAF)

- Border measured at least 3 different times separated by at least 6 month intervals

Goal is to demonstrate that the natural history has been altered

- 3 or more time points used to fit best curve or fit best line

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