Regulatory Perspective on Endpoints and Therapeutic Development

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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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