U.S. FOOD & DRUG ADMINISTRATION

Considerations for Endpoints for PML Clinical Trials

Virginia Sheikh, MD, CDER/OND/OID/Division of Antivirals

Focus of PML Endpoints Discussion

- Primary and other key endpoints
- Clinical trials designed to establish product efficacy and safety
- *Currently* available information

Important Characteristics of Clinical Trial Endpoints

- Well-defined
- Reliable
- Clinically meaningful
  - Direct measure of clinical benefit
  - Biomarkers that have been established as clinically meaningful endpoints (e.g., HIV viral load)
  - In some cases, biomarkers that are *reasonably likely* to predict clinical benefit can used to support approval via the accelerated approval pathway

* Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry. https://www.fda.gov/media/133660/download

Survival as an Endpoint

- Clinically meaningful, objective, and the "gold standard"
- May confer some disadvantages for PML clinical trials:
  - Does not capture full spectrum of serious and clinically meaningful PML clinical outcomes (e.g., being permanently bedbound)
  - Survival rates already high in certain patient groups (e.g., MS)
  - May require large sample size for an adequately powered clinical trial

Challenges to the selection of clinical endpoints beyond survival for PML

- Although neurologic progression is a clinically meaningful outcome, use of neurologic progression as an endpoint requires selection of reliable, well-defined, meaningful scale.
- Disability measures (e.g., functional scales) should adequately capture meaningful clinical outcomes in PML

Challenges to the use of biomarkers as clinical trial endpoints for PML

- Currently, no biomarkers have been established as predictors of clinical benefit in the setting of PML.
- The use of biomarkers (e.g., brain imaging and results of molecular tests) would have to be supported by strong scientific evidence supporting the biomarker's use as a predictor of clinical benefit.

Three Brief Talks to Inform PML Endpoints Discussion

PML disability outcome measures	Laura Baldassari, MD (FDA/CDER/Division of Neurology 2)
Brain imaging in PML	Mike Wattjes, MD (Hannover Medical School, Germany)
Evaluating the Potential for JCV DNA in Cerebrospinal Fluid as an Endpoint in Clinical Trials for PML Product Development	Irene Cortese, MD (NIH/NINDS) Gina Norato, Sc.M (NIH/NINDS) Paola Cinque, MD, PhD (San Raffaele Scientific Institute)

Speaker and panelist affiliations, disclosures, and bios are available meeting's webpage under "Meeting Materials": https://www.fda.gov/drugs/news-events-human-drugs/considerations-progressive-multifocal-leukoencephalopathy-clinical-trial-designs-09212021-09212021


FDA
U.S. FOOD & DRUG
ADMINISTRATION