U.S. FOOD & DRUG ADMINISTRATION

Considerations for Progressive Multifocal Leukoencephalopathy (PML) Clinical Trial Designs Virtual FDA Workshop

September 21, 2021

Opening Remarks, Workshop Overview, and Logistics

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PML – Unmet Need for Therapeutics

- Rare, opportunistic brain infection in patients with impaired cellular immunity
- Presents with a variety of neurologic symptoms including mental status changes, hemiparesis, gait ataxia, and visual symptoms
- Immune reconstitution (when possible) is the only effective treatment
- No approved or effective medical products

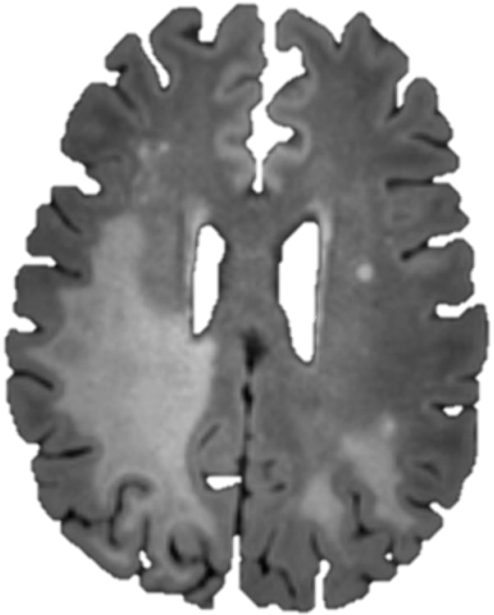

Image Courtesy of Dr. Daniel Reich.

PML Clinical Trial Design Challenges

- Rare
- Rapidly progressive, often fatal
- Diagnosis of PML often made late into presentation
- Neurologic presentation and course varies based on location and characteristics of brain lesions
- Natural history differs by underlying immune impairment and disease.
- Mobility and communications difficulties common

Workshop Purpose

The purpose of today's workshop is to foster an exchange of ideas on the challenges and clinical trial design considerations for developing products for the treatment of PML.

- Not product specific.
- Not for regulatory decision-making.
- All opinions, recommendations, and proposals are unofficial and nonbinding on FDA, NIH, and all other participants.

FDA/NIH PML Collaboration

- Collaborative effort between FDA, NINDS, and academic experts focused on facilitating the clinical development of effective therapeutic products for the treatment of PML. Project is product non-specific.
- Working groups established for each of 5 key areas of focus:
  - ❑ JC Virus Biomarkers
  - ❑ Brain imaging
  - ❑ Patient Focused Drug Development
  - ❑ Clinical Outcomes
  - ❑ Clinical Trial Design
- 2 main project aims:
  - ❑ Identify knowledge gaps and develop plans for filling gaps
  - ❑ Develop one or more Phase 3 PML clinical trial designs that may be acceptable to regulators, clinicians and patients — and that might foster industry engagement

Workshop Overview

Background	10:15am – 11:05pm EST
10-minute break	
Endpoints for PML clinical trials ▪ Panel Discussion	11:15am – 12:50pm EST
30-minute break (lunch)	
PML Patient Perspectives	1:20pm - 1:55pm EST
Selection of Control Groups ▪ Panel Discussion	1:55pm – 2:55pm EST
10-minute break	
PML Clinical Trial Designs ▪ Panel Discussion	3:05pm – 4:10pm EST

Workshop Logistics

- This meeting is being recorded. Speaker slides, transcripts, and recordings will be available for this meeting in the coming days.
- Speaker and panelist affiliations, disclosures, and bios are available on the meeting's webpage under "Meeting Materials".
- If you are not a workshop speaker or panelist, you microphone, and video are automatically be turned off.
  - Submit questions using the "**Q&A**" feature at the bottom center of your screen in Zoom.
  - Questions and comments submitted via the "Chat" will not be collated for Panelists.
- If you are experiencing any Zoom difficulties, please reach out to the Public Meeting Team at ONDPublicMTGSupport@fda.hhs.gov


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Background

JC Virus Virology and PML Pathogenesis	Eugene Major, PhD (NIH/NINDS)
PML Drug Development History, Current Standard-of-Care, and PML Therapeutic Landscape	David Clifford, MD (Washington University in St. Louis)
Clinical Outcomes among PML Patient Populations	Bryan Smith, MD (NIH/NINDS)

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