U.S. FOOD & DRUG ADMINISTRATION

Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Aimee Hodowanec at 240-402-5752.

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Surrogate Endpoints

- FDA anticipates that initial approvals for anti-HDV drugs will be based on a surrogate endpoint that is reasonably likely to predict clinical benefit
- An appropriate surrogate endpoint should provide evidence of both a decline in virologic replication and an improvement in associated liver inflammation as evident by biochemical response
- Following surrogate endpoint could be considered to support an accelerated approval:
  - Proportion of trial participants with undetectable serum HDV RNA (defined as <LLOQ), target not detected (TND)) and ALT normalization
- For drugs that are intended to be used as chronic suppressive therapy, a $\geq$ 2-$\log_{10}$ decline in HDV RNA and ALT normalization on-treatment could be considered an acceptable surrogate endpoint

Primary Endpoint Assessment

- Timing of the primary endpoint assessment will depend on the treatment strategy being evaluated (i.e., finite duration of therapy versus chronic suppressive therapy)
  - On-treatment after a predefined time period
  - At the end-of-treatment
  - Off-treatment after a specified duration of follow-up
- FDA encourages the sponsor to discuss its proposed primary efficacy endpoint and the timing of the endpoint assessment with the Agency.

Accelerated Approval (Subpart H) Considerations

- For HDV infection, no surrogate endpoints have been definitively shown to predict clinical benefit
- Trials aimed at demonstrating the clinical benefit of an HDV therapy would likely require a prolonged follow-up period
- FDA anticipates that development programs may opt to pursue accelerated approval pathways based on a surrogate endpoint reasonably likely to predict clinical benefit
- An accelerated approval pathway will require confirmation of clinical benefit through a long-term extension of the original trial or a subsequent additional clinical trial or trials
- Sponsors should consider planning for the confirmatory trial(s) during the development of the phase 3 program

Providing Comments on Draft Guidance

- We encourage stakeholders to provide comments on the Draft Guidance
- The FDA Draft Guidance can be accessed at: https://www.fda.gov/media/132137/download
- Electronic and written comments will be accepted through December 31, 2019. Please see the Federal Register for further instructions https://www.federalregister.gov/documents/2019/11/01/2019-23926/chronic-hepatitis-d-virus-infection-developing-drugs-for-treatment-draft-guidance-for-industry

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Thank you!

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