Trial Design (Flares and Mitigating Risk): FDA Perspective

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Stopping NUCs in Drug Development

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Disclaimer

- No conflicts of interest
- This presentation reflects the views of the speaker and should not be construed to represent FDA views or policies

Outline

- Trial Design
- Safety Monitoring
- Hepatic Flares
- Liver Safety Assessment
- HBV Treatment Discontinuation
- Stopping NrtI Therapy

Trial Design

Adequate and Well Controlled Studies 21 CFR 314.126 (b)

- Randomized, active-controlled design allows direct comparison
- Trials to demonstrate superiority: the new product is *superior* to the control
- Trials to demonstrate Non-inferiority (NI): the new product is *not unacceptably worse* than the active comparator, based on a pre-specified NI margin (M)

Trial Design Considerations

- Appropriate trial design depends on the patient population being studied and the treatment regimen being evaluated
  - Investigational drug vs. Placebo – feasible in population with inactive disease in whom treatment is not recommended (*per current treatment guidelines*)
  - Investigational drug vs. NrtI or IFN alone (active control) – in patients with active disease
  - Add-on to current therapy – in patients virally suppressed on NrtIs (Investigational drug + current Rx vs. Placebo + current Rx)

Benefit-Risk Assessment in Drug Regulatory Decision Making

"To be approved for marketing, a drug must be **safe and effective** for its intended use."

- Effectiveness requirement:
  - Demonstrates "substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use" (21CFR314.125, 21CFR314.126)
- "Safe" for use:
  - Interpreted as the determination that a **drug's benefits outweigh its risks** to the intended population
- Benefit-Risk Assessment:
  - benefits outweigh potential risks to the intended population

FDA's Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severity of the underlying condition • How does it affect patients' daily life • Any key gaps in the understanding of this condition	
Current Treatment Options	• How well the patients' medical needs are addressed by currently available therapies • Effectiveness, safety, and tolerability of these therapies • Any benefits provided over existing therapies	Provides context for weighing the drug's benefits and risks
Benefit	• Clinical relevance of the endpoints • Magnitude and durability of the effect(s) • Any notable variability in efficacy across subpopulations	
Risk and Risk Management	• Overall understanding of product's safety profile • Most important safety concerns • Any identified serious safety concerns that may require risk management beyond product labeling	Drug-specific assessments based on available evidence from clinical data

Conclusions Regarding Benefit-Risk for Regulatory Decisions

Safety Monitoring in Phase 2/3 Trials

Key Considerations

- Protocols should include safety monitoring plans based on
  - nonclinical data, PK/PD, and observed safety profile in early phase trials
- Dose-escalation approach
  - safety should be demonstrated at the lower doses prior to dose escalation
- Staggered enrollments into cohorts based on
  - demonstrated safety in the earlier cohorts
- Drug-drug interaction
- Target population
- Dose limiting toxicity
- Dose modification guidelines
- Stopping criteria for subjects and for trial
- Specific safety monitoring based on safety issues in drug class
- Potential for overlapping toxicities with individual drugs in the combination regimen
- Interim safety assessments
- Independent Data Safety Monitoring Boards
- Need for additional studies premarket/postmarket

PK/PD: pharmacokinetic/pharmacodynamic

Hepatic Flares

- Assessing causation of ALT flares is challenging
  - "immune-associated or antiviral flares" - due to host immune responses, accompanied by decline in HBV DNA and viral antigen levels
  - "virus-induced flares" - due to enhanced viral activity, either related to a lack of efficacy or drug resistance
  - "drug-induced flares" - due to undesired effect of drug, such as autoimmunity or DILI
- Predicting the severity of hepatic flares due to activation of intrahepatic immunity
  - Close monitoring of ALT elevations is necessary to monitor trends
  - Prespecified criteria for defining/monitoring hepatitis flares during treatment and after stopping therapy
  - Severe flares with deterioration in hepatic function can be serious and life-threatening, particularly in patients with advanced disease
  - Adverse events of death, liver transplantation, hepatic decompensation, irreversible autoimmunity, or severe hepatitis flare – *major safety concerns*

Cornberg M, et al. Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. Hepatology. 2019 Nov 12

Liver Safety Evaluation – HBV Forum Initiative

Multi-stakeholder participation – academia, industry, and FDA

NON-COMMISSIONED REVIEW

Liver safety assessment in clinical trials of new agents for chronic hepatitis B

Robert J. Fontana, Mark I. Avigan, Harry L. A. Janssen, Arie Regev, Poonam Mishra, Anuj Gaggar, Nathaniel Brown, Cynthia Wat, Patricia Mendez, Ryan T. Anderson, Bruce Given, Veronica Miller, Maria Beumont ... See fewer authors

Liver Safety Assessment

- Frequent monitoring of liver safety biomarkers during trials
- Prespecified algorithmic approach to the evaluation and management of liver safety signal
  - Interpretation of serum ALT flares in the context of other biomarkers such as HBV DNA, bilirubin, INR, albumin levels
  - Incidence and severity of liver safety biomarkers
  - Presence of extrahepatic features such as fever, rash or eosinophilia
  - Treatment dose or duration effect
  - Baseline liver disease parameters
  - Rule out alternative causes of liver injury
- Study drug interruption or discontinuation criteria
- Role of independent expert adjudication panel in assessing drug's hepatotoxicity profile during clinical development

Fontana et al. J Viral Hepat. 2020 Feb;27(2):96-109

HBV Treatment Discontinuation

- In general, off-treatment when evaluating investigational "finite duration" therapies refers to discontinuation of all therapies (i.e., investigational agent and background NrtI regimen)
- Criteria for stopping therapy at the end of the investigational treatment period
  - Should be well-defined in the protocol and should be discussed with the FDA in advance of trial initiation
  - Should be based on clinically validated biomarkers to mitigate potential risk to trial participants
  - Use of *novel* biomarkers as a trigger for treatment interruption should be supported by strong scientific rationale
  - Scientific consensus is needed on appropriate stopping criteria in the context of clinical trials
- Known and potential risks of investigational drug, as well as pharmacokinetic and pharmacodynamic characteristics, should inform additional safety monitoring and duration of follow-up

Stopping NrtI Therapy

- Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV therapy, particularly in the absence of HBsAg loss
  - Treatment discontinuation should initially be evaluated in subpopulations with low risk of HBV flare/serious hepatic outcomes
  - Pre-specified criteria/plan for frequent clinical and laboratory monitoring for HBV flares after discontinuation of anti-HBV therapy
  - Stringent criteria/detailed plan for HBV treatment reinitiation for flares should be included in the protocols
- Criteria for stopping NrtI therapy should be based on clinical evidence that also reflects current practice guidelines
  - To ensure that the discontinuation of effective NrtI therapy does not pose undue safety risk to the trial participants
- Long duration of follow-up for patients who remain off-therapy, both for safety assessment and durability of response
  - May vary based on the mechanism of action and half-life of specific investigational drug

NrtI: HBV Nucleoside/nucleotide reverse transcriptase inhibitor

Patient's Voice in Drug Development

HEPATITIS B FOUNDATION

The Voice of the Patient Report

Living with Chronic Hepatitis B

Meeting date: June 9, 2020

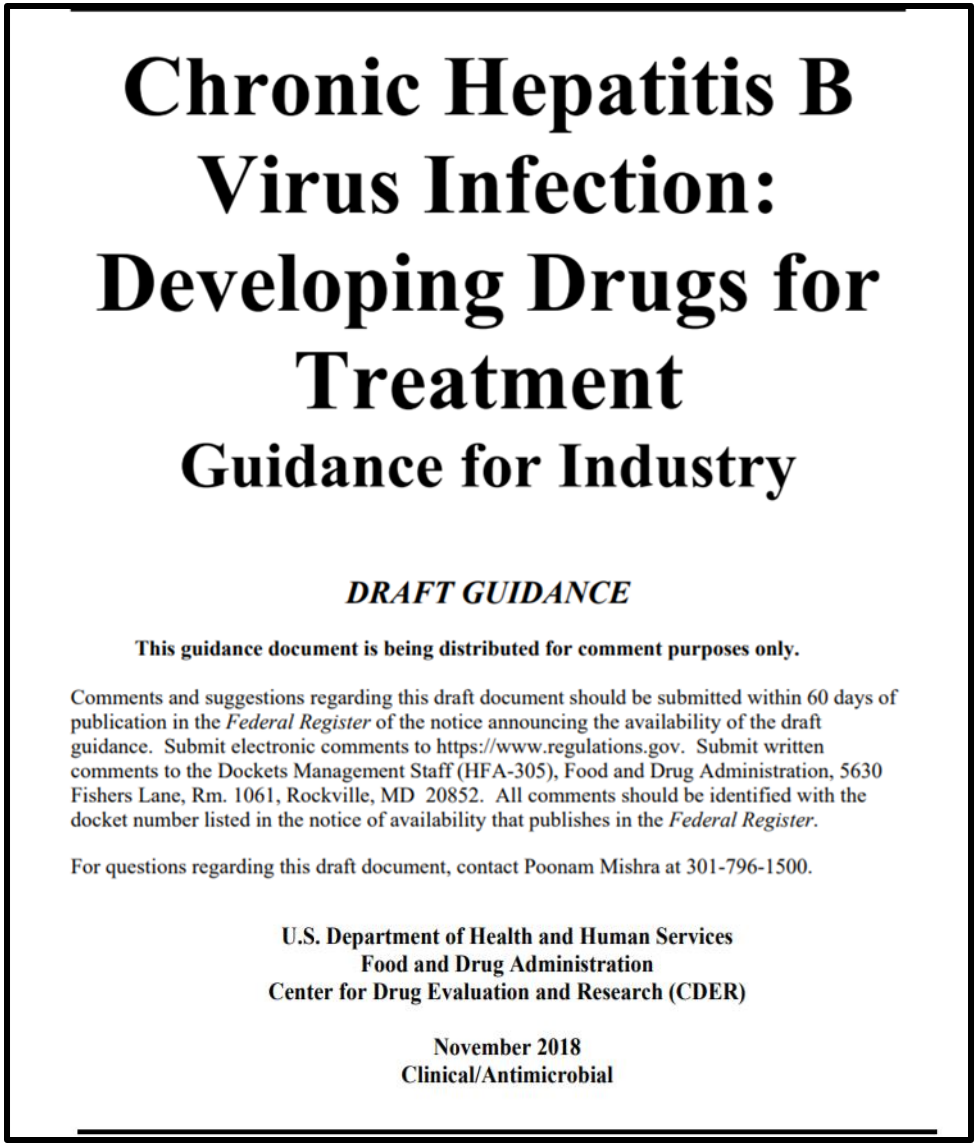
Report Date: October 2020

Enhancing understanding of patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

https://www.hepb.org/assets/Uploads/ExPFDD-Report-HBF-10-1-2020.pdf

Draft Guidance for Industry



Chronic Hepatitis B 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 Poonam Mishra at 301-796-1500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2018
Clinical/Antimicrobial

Resources

- Division of Antivirals Pre-IND Consultation Program

  https://www.fda.gov/drugs/pre-ind-consultation-program/division-anti-viral-dav-pre-ind-letter-instruction

- Draft Guidance for Industry – "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products", December 2017

  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf

- Draft Guidance for Industry – Chronic Hepatitis B Virus Infection: Developing drugs for Treatment, November 2018

  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM624695.pdf

Conclusions

- Benefit-risk assessment is the foundation for the FDA's regulatory review of human drugs and biologics
- Multidisciplinary assessment of safety risks continues throughout the drug's lifecycle
- Avoiding unreasonable and significant risk to clinical trial participants and patients is paramount
- Collaborative discussions between academia, industry, regulatory agencies, and patient advocacy groups are crucial for efficient drug development
- FDA remains committed to facilitate the development of safe and effective therapies for people living with chronic HBV infection globally

Working together to achieve Hepatitis B Elimination!

Thank you!

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