Berkeley School of Public Health

FORUM for Collaborative RESEARCH

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Welcome and Introductory Remarks

Hepatitis B Foundation and HBV Forum Meeting with DAVP, FDA March 20, 2017

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The information in these slides is derived from notes and understanding of Foundation-Forum meeting attendees, and does not comprise official meeting minutes.
Unofficial meeting minutes can be distributed at the request of interested parties.

Introduction

- Meeting was granted Debra Birnkrant, MD, Director of Division of Antiviral Products (DAVP), FDA at the request of Nathaniel Brown, MD, on behalf of the Hepatitis B Foundation (HBF) and HBV Forum
- Aim was to discuss efficient clinical development programs for new, potentially curative HBV therapies

Objectives

- Discuss the status of the DAVP's new draft guidance on HBV Drug Development
- Interactive discussion with DAVP on issues related to clinical development of new HBV therapeutics to potentially increase the proportion of patients achieving therapeutic responses that are durable following a limited treatment duration
  - SVR off treatment
  - loss of HBsAg

Disclaimer

- This meeting summary is based on the notes and understanding of the HBF and the HBV Forum attendees
- This presentation not been reviewed or endorsed by the the DAVP, FDA

Attendees at DAVP Meeting

- HBF Attendees
  - Timothy Block, PhD
  - Nathaniel Brown, MD
  - Carol Brosgart, MD
    - dial-in
  - Robert Gish, MD
    - dial-in
- HBV Forum Attendees
  - Veronica Miller, PhD
  - Pedro Goicochea, MSc
- DAVP Attendees
  - Jeffrey Murray, MD, MPH, Deputy Director
  - Poonam Mishra, MD, Deputy Director for Safety
  - Kim Struble, PharmD, Medical Team Leader
  - Julian J. O'Rear, PhD, Virology Team Leader
  - And ~ 15 other DAVP staff

Meeting Summary

- Collaborative and far ranging discussions
- Mutual enthusiasm about the number of agents in development for possible HBV cure or functional cure
- Discussed recent FDA, AASLD, and EASL HBV Endpoints meeting in DC, September 2016
- New FDA HBV Drug Development Guidance
  - Will be released for comment in late 2017 or early 2018
  - HBF and HBV Forum attendees offered assistance to DAVP in development of this guidance

Drug-Drug Interaction Studies

- **What will be the requirements for completing clinical drug-drug interaction (DDI) studies for an investigational agent (drug X) with nuc(s), before treating nuc-suppressed pts with a drug X + nuc combination regimen in Phase 1b-2a trials?**
  - The 5 licensed HBV nucleos(t)ide polymerase inhibiting drugs (nucs) are now available, generically, in most countries
  - Recruitment of treatment-naïve patients is presently challenging

Phase 1b-2a POC Studies

- Enroll and treat nuc-suppressed patients in early Phase 1b-2a proof-of-concept (POC) trials of investigational HBV agents
  - Nuc suppressed HBV patients are the patients available at most large centers, in developed nations, for new clinical trials
  - Inactive carriers are currently not recommended for treatment by the AASLD, EASL, and APASL practice guidelines.
  - Requested DAVP clarification about when a clinical DDI study might be required before treating nuc-suppressed patients with investigational agent X added to ongoing nuc therapy, in early (Phase 1b-2a) trials of new agents
  - DDI studies associated with increased cost and delay in development timelines

DDI Response by DAVP

- Clinical DDI study appropriate if the new investigational agent shares metabolism or clearance pathways with the patient's current nuc therapy
  - *If available preclinical data and Phase 1a clinical data (safety/PK) are sufficient to address the above concerns, DAVP is not expected to routinely require clinical DDI*

- Will need preclinical virology evidence supporting a lack of antiviral antagonism between the new agent and the targeted nuc therapies, before adding a new investigational agent in combination with ongoing nuc therapies

Duration of Phase 1b, First-in-Patient Protocols

- Phase 1b trials of the current licensed HBV nucs employed treatment durations of 4 weeks, allowing observation of initial 1st and 2nd phase HBV DNA responses
- Longer Phase 1b treatment periods may be needed for initial assessments of dose-related efficacy of new investigational agents in nuc-suppressed patient populations, or for investigation of agents with expected slower mechanisms of action
  - HBV DNA changes may be difficult to discern (e.g. in nuc-suppressed patients)
  - Longer-term efficacy effects are more important
    - Quantitative changes in serum HBeAg and/or HBsAg
    - Changes in immune response markers, etc.
- Would DAVP would allow Phase 1b protocols in which, at Sponsor request, patient exposures to the investigational agent could be as long as 12 weeks?
  - Assumes that supportive 12-week animal toxicology data are submitted with (or prior to) the Phase 1b protocol.
- *DAVP staff indicated that longer Phase 1b treatments could be acceptable for appropriately-selected Phase 1b patient populations*
  - *If preclinical data (including 12-week animal tox data) and*
  - *Phase 1a PK and safety data were supportive of 12-week patient exposures*

Will General Requirements for Clinical Trials of HBV Combination Therapies be Similar to the DAVP published HIV and HCV Guidance criteria?

- Preclinical combination toxicology : ICH M3 guidance on non-clinical safety studies will be the generally applicable regulatory guidance regarding animal combination toxicology studies required to support clinical protocols in which one or more of the drugs in the combination regimen is investigational
- FDA staff commented that preclinical combination tox studies in animals would generally not be needed for clinical studies of one new agent combined with an approved agent, unless preclinical or clinical data for the new agent suggested the possibility of PK/PD interactions for the new agent with the approved agent(s)
- For clinical protocols assessing combination regimens with two or more investigational agents, FDA staff commented that, per the ICH M3 guidance, combination toxicology studies would typically be required, with the combination treatment of study animals typically conducted for up to 12 weeks.
- **Conclusion**: *The ICH M3 guidance on non-clinical safety studies will be the generally applicable regulatory guidance for animal toxicology data needed to support clinical protocols with one or more investigational agents*

Data Requirements for Clinical Protocols with Investigational Combination Therapies

- *Evolving HBV drug development guidance will probably be similar to previous HIV and HCV drug development guidance documents*
  - *Each of the investigational agents to be used in investigational combination regimens should minimally have sufficient early clinical data (Phase 1a-1b/2a safety, PK, and preliminary efficacy data), with preclinical data (tox and virology) and early clinical data supporting the rationale for studying the two investigational agents in combination*
- *For double-investigational clinical regimens, animal combination tox studies will generally be required, in addition to standard requirements for sufficient GLP tox data for the individual investigational agents*
- *Also, clinical DDI studies will be needed if data suggests that drug interactions are a potential risk based on preclinical data or early clinical data for the investigational agents*

Transitioning from Phase 1b HBV Trials to Phase 2 Protocols

- 1st HBV licensed nucs developed by large biopharma companies (GlaxoWellcome/GSK, BMS, Idenix-Novartis, Gilead) who could afford to initiate chronic animal tox studies “at risk”, before supportive Phase 1a/1b clinical data were available to support advancement to Phase 2
- Today, many companies with potentially innovative HBV drugs are small biotech companies with limited funding who are generally reluctant to initiate expensive chronic animal tox studies “at risk” before supportive Phase 1a-1b clinical data are available
- Potential significant delay (perhaps 6-12 months or more) in initiation of Phase 2 trials of new agents with promising Phase 1a-1b data

Challenge for Safety

- Clinical protocols can be written to require treatment discontinuation for patients or treatment groups that do not meet specified treatment tolerance criteria. Dr Murray and Agency staff considered this idea but felt that, even with supportive 12-week preclinical tox, ongoing chronic tox studies, supportive early clinical data, and protocol-stipulated safety/tolerance criteria, there could be unpredictable risks for sudden and serious adverse events in patients, sometimes many weeks into Phase 2 treatment
  - The tragic example of delayed Phase 2 cardiotoxicity with BMS' HCV nucleoside (BMS-986094, formerly INX-189) was cited, in which one patient died and eight others had severe cardio-renal toxicity
- **DAVP Conclusion**
  - *Based upon previous experiences, proposals to initiate long-term Phase 2 treatment arms before completion of chronic tox studies would probably not be regarded favorably in Agency reviews of future Phase 2 HBV clinical protocols.*
  - *The implication of this discussion is that, if HBV sponsors seek to minimize delays in clinical program transition from Phase 1b to 2, they should proactively gain Agency agreement on GLP chronic tox protocols for their investigational agent and should initiate the agreed chronic tox studies soon after Phase 1 clinical studies are underway, unless an unusually long timeline is expected for Phase 1a-1b clinical POC studies.*

Endpoints for Enhanced Sustained Response Rates in Phase 3 Registration Trials

- Previous standard primary efficacy endpoint (e.g., non-inferior maintained HBV DNA suppression and ALT normalization, with or without histologic response data), and with secondary efficacy endpoints corresponding to sustained response achievements (e.g. sustained for at least 24 weeks off-treatment) or loss of HBsAg
- **Conclusion**
  - *There was limited time available during the meeting to fully explore a potential pathway to (secondary) sustained response claims*
  - *Agency staff considered these ideas but it was unclear whether they would recognize priority for Phase 3 protocols that have standard primary efficacy endpoints, as priority is usually given to registration trials that can demonstrate a "therapeutic advance" based on Phase 3 primary endpoint data.*

ALT "Flare" Phenomena in Clinical Trials of New HBV Agents

- Four types of ALT flares reported for HBV patients in the medical literature
  - Spontaneous ALT flares, during the natural history of chronic HBV
  - Three types of ALT flares observed in clinical trials
    - Early on-treatment flares (first 3 months) most often "good" flares, associated with good initial virologic responses (rapid multi-log HBV DNA reductions).
      - Early on-treatment ALT flares can sometimes be quite high (e.g. ALT 1-3,000 IU/L)
      - These flares are generally not associated with declining hepatic synthetic function (decreasing abumin) or declining excretory function (increasing bilirubin).
      - Important in HBV trial protocols to recognize patients with early ALT flares and institute closer monitoring of such patients, but to not discontinue patients if close monitoring indicates no change in hepatic functions and the investigational agents have low risk for hepatotoxicity
    - Later on-treatment flares
    - Post-treatment flares
      - May be seen with other mechanisms of action than nuc HBV DNA suppression or with agents for which preclinical toxicology or early clinical data suggest an appreciable potential for hepatoxicity
      - ALT flares with immunomodulatory agents that enhance cytotoxic immune responses to HBV-infected hepatocytes may present risks for hepatic decompensation in circumstances of potent killing of infected hepatocytes or when hepatic functional reserve is limited by advanced fibrosis.

ALT Flare Perspective from DAVP

- *The DAVP response regarding handling of ALT flares in clinical protocols was led by Poonam Mishra,* Deputy Director for Safety
  - *Close monitoring of patients with ALT flares is deemed appropriate*
  - *For agents with a low potential for hepatotoxicity (other than immunomodulators), the evolving HBV drug development guidance will likely not recommend arbitrary discontinuation of trial patients with early ALT flares, as long as close monitoring indicates no significant changes in hepatic function*

Questions