SUMMARY REPORT
Hepatitis B Foundation and HBV Forum Meeting
with the
U.S. Food and Drug Administration (FDA)-Division of Antiviral Products (DAVP)

March 20, 2017 – 1:00 – 2:30 pm
FDA Headquarters, Silver Spring, MD
Conference Room 1311, Building 22

Hepatitis B Foundation Attendees
Timothy Block, PhD, President
Nathaniel Brown, MD, Board Member
Carol Brosgart, MD (dial-in), SAB Member
Robert Gish, MD (dial-in), Medical Director and SAB

HBV Forum Attendees
Veronica Miller, PhD, President
Pedro Goicochea, MSc, Sr. Research Associate

FDA-DAVP Attendees
Jeffrey Murray, MD, MPH (Deputy Director)
Poonam Mishra, MD (Deputy Director for Safety)
Kim Struble, PharmD (Medical Team Leader)
Jules O'Rear, PhD (Virology Team Leader)
And about 15 other FDA-DAVP staff

Disclaimer: This meeting summary, prepared by Drs. Nat Brown and Tim Block, represents the recollections and perspectives of the Hepatitis B Foundation & HBV Forum attendees and should not be considered to be formal, FDA-approved meeting Minutes.

The March 20, 2017 meeting was granted by Dr. Debra Birnkrant, Director of the FDA Division of Antiviral Products (DAVP), at the request of Dr. Nat Brown on behalf of the Hepatitis B Foundation (Foundation) and the HBV Forum (Forum). With the ongoing high global mortality of HBV infection, it is important that clinical development programs for more-curative HBV therapies should be time- and resource-efficient.

This meeting summary represents the notes and understanding of the Foundation & Forum attendees and should not be considered to comprise formal FDA-approved meeting minutes. When sponsors are contemplating regulatory dimensions of specific HBV clinical development issues, including the issues discussed here, they should utilize appropriate pathways for FDA input when needed - e.g. pre-IND, end-of-Phase 2, or pre-NDA interactions, or informal review requests.

The meeting goals for Foundation & Forum attendees were:

1. To learn the status of FDA-DAVP's draft of an HBV Drug Development Guidance; and
2. To engage FDA-DAVP staff in an interactive discussion of several issues related to clinical development of new HBV therapeutics targeted to substantially increasing the proportion of patients achieving therapeutic responses that are durable post-treatment.

The Agenda topics sent in advance to FDA-DAVP were related to new practical issues for HBV clinical drug development that have arisen in the past decade, subsequent to circumstances that prevailed during the development of HBV nucleos(t)ides (ca. 1993-2006).

Overall, DAVP representatives were accommodating and open to informal discussion of our Agenda topics. DAVP attendees indicated that such meetings, and other more formal meetings, such as the recent Endpoints symposia jointly held by AASLD and EASL in September (2016), are helpful to their regulatory deliberations. They were also interested in seeing manuscripts in scholarly journals dealing with HBV clinical trial endpoints, and they look forward to attending upcoming meetings of HBV experts. To facilitate drafting of their regulatory guidance regarding development of new HBV therapeutics, they anticipate using their experience with other antiviral development programs, including previous HBV programs, and they appreciated the challenges of clinically assessing new HBV therapeutics with novel mechanisms of action.

Outcomes for the Agenda discussion points were as follows:

Current status of DAVP's HBV drug development guidance?

Drs. Murray and Mishra indicated that a first draft of the planned HBV drug development guidance, mentioned at the Sept 2016 AASLD/EASL meeting on HBV Endpoints, will likely not be released for comment until late 2017 or sometime in 2018. DAVP is working through a number of issues relevant to HBV drug development, including deliberations about which topics should be included for comment in the planned HBV guidance. The Foundation & Forum meeting participants offered a commitment to provide `external stakeholder' input to DAVP's issued drafts of the the HBV drug development guidance, as they become publicly available for review.

What will be the requirements for completing clinical drug-drug interaction (DDI) studies for investigational drug X with nuc(s), before treating nuc-suppressed pts with a drug X + nuc combination regimen in Phase 1b-2a trials?

The first 5 HBV nucleos(t)ide polymerase inhibiting drugs (nucs) are now available generically in most countries. Consequently, at large Asian and "Western" clinical centers, including those that were high enrollers in previous HBV treatment trials, most currently-diagnosed patients are promptly started on suppressive nuc therapy, usually manifesting good tolerance and low HBV DNA levels. Treatment-naïve patients are the preferred patient group for early proof-of-concept trials, due to rapid readout of HBV DNA changes. But recruitment of treatment-naïve patients is presently challenging, as it depends on finding newly-diagnosed patients fitting treatment criteria who can be persuaded to enroll in a commitment-intensive trial of an unproven agent before receiving standard therapy.

It is, therefore, desirable to be able to enroll and treat nuc-suppressed patients in early (Phase 1b-2a) proof-of-concept (POC) trials of new HBV agents, as they are the largest readily available HBV patient group at most large centers in developed nations, aside from inactive carriers (who are currently not recommended for treatment by the AASLD, EASL, and APASL practice guidelines). Adding an investigational agent to a patient's existing nuc therapy raises the issue of possible drug interactions, the potential for which is usually investigated in preclinical studies of new drug candidates.

The query for DAVP staff at this meeting involved clarification of circumstances when a clinical drug-drug interaction (DDI) study might be required before treating nuc-suppressed patients with investigational drug X added to patients' nuc therapy, in early (Phase 1b-2a) trials of new agents. Such clinical DDI studies typically cost $400-700K and require about 6 months' operational time (initial planning through preliminary study report), comprising a potentially significant delay in Phase 1b-2a clinical timelines.

FDA staff, led by Dr. Murray and two FDA pharmacologists, indicated that the Agency requirement for a clinical DDI study, before treating nuc-suppressed patients with an add-on

investigational HBV agent, would typically be based on currently prevailing criteria for investigational combination therapies; i.e. a clinical DDI study would be seen as appropriate if the new drug shared metabolism or clearance pathways with the patient's nuc therapy, which might significantly alter the patient's systemic nuc exposures or could engender risks related to systemic exposures of the investigational agent higher than exposures evaluated in previous clinical and preclinical studies. Dr. O'Rear added that, from a Virology perspective, he would want to see preclinical information supporting a lack of antiviral antagonism between the new agent and the targeted nuc therapies, before condoning treatment of nuc-suppressed patients with the new agent in a combination regimen with patients' nuc therapies.

> Conclusion: *This group discussion was helpful in assuring that, with available preclinical data and Phase 1a clinical data (safety/PK) sufficient to address the above concerns, DAVP is not expected to routinely require clinical DDI studies before allowing add-on treatment of nuc-suppressed patients with new HBV agents, in early trials.* On the other hand, new agents that depend on substantial renal clearance (the major nuc clearance route), or which have potentially interfering effects with nucs due to GI or hepatic transporter interactions, or which have potential safety-related PK/PD interactions, in principle could require clinical DDI studies (new agent + nuc) before treating nuc-suppressed patients with the new agent in combination with the patients' nuc therapies. To avoid a negative timeline impact for conducting an unplanned DDI study during the early (Phase 1b-2a) critical path, sponsors who might need Agency clarification regarding a possible need for clinical DDI studies could include this issue in a pre-IND or timely Phase 1a IND submission, for Agency review and discussion.

Can Phase 1b (first-in-patient) protocols employ treatment arms as long as 12 weeks, rather than previously conventional 2-4 week Phase 1b patient exposures?

Phase 1b trials of HBV nucs commonly employed treatment durations of 4 weeks, allowing observation of initial first- and second-phase HBV DNA responses. In the current era, investigation of new agents in nuc-suppressed patient populations, or investigation of agents with expectedly slower mechanisms of action, longer Phase 1b treatment periods may be needed for initial assessments of dose-related efficacy - especially when HBV DNA changes are difficult to discern (e.g. in nuc-suppressed patients) or are of secondary interest, and longer-term efficacy effects are more important (e.g. quantitative changes in serum HBeAg and/or HBsAg, or changes in immune response markers, etc). The meeting Agenda queried whether DAVP would allow first-in-patient (Phase 1b) protocols in which, at Sponsor request, patient exposures to the investigational agent could be as long as 12 weeks - assuming that supportive 12-week animal toxicology data are submitted with (or prior to) the Phase 1b protocol.

> Conclusion: *FDA-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 criteria previously promulgated in DAVP's HIV and HCV drug development guidances?

Preclinical combination toxicology: FDA-DAVP staff commented that the ICH M3(R2) 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(R2) 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(R2) 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:

> Conclusion: *Agency staff commented that, with regard to clinical protocols proposing novel combination regimens, the evolving HBV drug development guidance will probably be similar to previous HIV and HCV drug development guidances, which require that each of the investigational agents to be used in such an investigational combination regimen 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. As noted above, 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, the aforementioned discussion of when clinical DDI studies will be needed suggests potential requirements for clinical DDI studies if drug interactions are a potential risk based on preclinical data or early clinical data for the investigational agents.*

In the transition from relatively short Phase 1b trials to Phase 2 protocols with longer treatment durations, can the longer Phase 2 patient treatments (e.g., 1 year) be started after filing supportive (Phase 1a-1b) clinical data and supportive preclinical tox data (with animal treatment durations ≥12 weeks), in circumstances where chronic animal tox studies are ongoing but are not yet completed?

In the previous era of HBV nuc development, corporate sponsors were typically sizeable Pharma companies with revenue streams (GlaxoWellcome/GSK, BMS, Idenix-Novartis, Gilead) who, in anticipation of Phase 2 preclinical data needs, 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. In the current era, many companies with potentially innovative HBV drugs are small biotech/pharma with limited funding and no large corporate partners, who are generally reluctant to initiate expensive chronic animal tox studies "at risk" before supportive Phase 1a-1b clinical data are available. This situation creates a potentially significant delay (perhaps 6-12 months or more) in initiation of Phase 2 trials of new agents with promising Phase 1a-1b data. On a few past occasions with pressing needs for new life-saving therapies, FDA allowed initiation of one-year treatment regimens for new agents as long as the antecedent preclinical and clinical data were supportive and chronic animal tox studies were ongoing (but not yet completed). Such 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.

> Conclusion: FDA-*DAVP staff felt that, 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 proof-of-concept studies.

To achieve product label claims for enhanced sustained response rates, could Phase 3 registration trials be conducted with a 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 post-treatment)?

Such secondary sustained response endpoints in Phase 3 protocols would be based on suggestive Phase 2 data, but would be indicated as secondary (not primary) Phase 3 efficacy endpoints due to statistical uncertainties associated with limited Phase 2 datasets. In recent years a limited array of secondary efficacy claims, based on protocol-specified secondary efficacy endpoints, have been allowed if Phase 3 data satisfy study postulates on the primary efficacy endpoint and the Phase 3 data also meet pre-specified confidence intervals for hierarchically prioritized secondary endpoints in Agency-allowed clinical protocols. For sponsors concerned about the large costs of a Phase 3 trial program, use of a `standard' primary efficacy endpoint, with sustained response endpoints included as hierarchically prioritized secondary endpoints, improves the chances for at least achieving product registration with certain types of Phase 3 designs - e.g., nuc + agent X vs. nuc alone (or nuc + agent X placebo). The sponsor's downside for this approach to product registration is the risk of lack of a differentiating product label, if Phase 3 data are not strong enough for label claims based on the secondary sustained response endpoints.

Conclusion: *There was limited time available during the meeting to fully explore this 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.*

The final discussion explored how Agency staff might address the issue of ALT "flare" phenomena in clinical trials of new HBV agents, in drafting the HBV drug development guidance and in reviewing clinical protocols for new HBV agents.

ALT flares have unique considerations for HBV patients, with four types of ALT flares reported for HBV patients in the medical literature, as mentioned in the pre-circulated meeting Agenda: spontaneous ALT flares, during the natural history of chronic HBV infection, and three types of ALT flares observed in clinical trials: early on-treatment flares (first 3 months), later on-treatment flares, and post-treatment flares. Early on-treatment flares have been observed in interferon and nuc trials. With these antiviral agents, early ALT on-treatment flares are most often "good" flares, associated with especially good initial virologic responses (rapid multi-log HBV DNA reductions). With early on-treatment flares absolute ALT levels can sometimes be quite high (e.g. ALT 1-3,000 IU/L) but these flares are generally not associated with declining hepatic synthetic function (decreasing abumin) or declining excretory function (increasing bilirubin). Consequently, it is important in HBV trial protocols to recognize patients with early ALT flares and institute closer monitoring of such patients, but to not discontinue such patients if close monitoring indicates no change in hepatic functions and the investigational agents have low risk for hepatotoxicity.

The group discussion noted that this relatively benign perspective on early ALT flares with HBV nuc and interferon therapies is not necessarily applicable to agents with other mechanisms of action, or with agents for which preclinical toxicology or early clinical data suggest an appreciable potential for

hepatoxicity. Especially, 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.

> Conclusion: *The Agency response regarding handling of ALT flares in clinical protocols was led by Dr. Mishra (FDA-DAVP). She indicated that intercurrent evaluation and close monitoring of patients with ALT flares is deemed appropriate, but 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.*

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