HBV Forum 3 Summary Report
October 24th, 2017
Washington DC

Welcoming Remarks

Slides: Welcoming and Introductory Remarks

Presenter: Pedro Goicochea, Forum for Collaborative Research

Operating principles: All members of the Forum have equal voice and co-ownership of this process and what happens within the Forum. There are plenty of opportunities for open discussions and deliberation, but what is said in the Forum stays at the Forum. Regarding participation of industry stakeholders, participation is not contingent to financial support, and we encourage companies to send scientists and clinical researchers.

- The forum has a steering committee with 22 representatives from academia, industry, community representatives, regulators and foundations. We have launched and developed the work of the HBV Forum under three working groups. The first working group is the Diagnostics & Biomarkers, co-chaired by Ed Marins and Gavin Cloherty; the Surrogate Endpoints working group, co-chaired by Marion Peters and Oliver Lenz; and the Treatment Combination working group, co-chaired by Bruce Given and Professor Seng Gee Lim. Also, under the wing of the Treatment Combination working group, a new working group co-chaired by Maria Beumont and Robert Fontana will be working on discussing issues regarding drug-induced liver injury and flares in the context of HBV drug development.
- Since November of 2016, the number of members of the HBV Forum has more than doubled from 78 to 158. There are currently 35 companies participating in the HBV Forum, of which 14 are financially sponsoring the activities of the HBV Forum.

Considerations in HBV Drug Development: FDA Perspective

Slides: Current FDA perspective on HBV Drug Development

Presenter: Poonam Mishra, Division of Antiviral Products, FDA

- This presentation is intended to provide a high-level, generally applicable approach to trial designs and trials of efficacy endpoints.
- Current thinking of the FDA is very much aligned with the consensus statement produced from the collaborative workshop organized by the AASLD and EASL in September of last year, which was published in both in *Hepatology* and *Journal of Hepatology* simultaneously.
    - Development of new therapies is targeted to achieve HBV cure, that is, elimination of HBV cccDNA from all HBV infected cells. The goal of novel HBV therapies is aimed at finite duration of therapy with no risk of virologic relapse and minimal risk of liver disease progression after the cessation of therapy. However, there are many challenges in reaching this goal. HBV cccDNA can persist in the liver in individuals who have recovered from acute HBV infection. HBV reactivation can occur in so-called recovered individuals when they are immunosuppressed. HBV DNA is integrated into the host genome. Hence, complete HBV cccDNA clearance from the host or complete sterilizing cure may not be a feasible goal.

  - Some other proposed definitions of HBV cure were also discussed at the AASLD/EASL workshop. A state of functional cure that is sustained undetectable HBV DNA in serum and hepatitis B surface antigen loss with/without anti-HBs seroconversion after a finite course of therapy has been discussed as a feasible goal. Partial cure has been proposed as a reasonable intermediate goal and is characterized as persistently undetectable HBV DNA in serum but detectable surface antigen after completion of a finite course of treatment, achieving so-called inactive carrier state but off therapy.
- Minimal proof of principle need to be demonstrated in early phase trials. Perhaps, it would be better to think about the endpoints for these early phase trials in terms of impact on biomarkers of biological activity and not as an assessment of efficacy per se.
  - Exploratory endpoints in early phase trials may be helpful in defining efficacy endpoints for later phase trials.
- General information recommended to support phase 2 trials of combination therapies.
  - Mechanism of action of each drug in the combination regimen.
  - Combination antiviral activity data from cell culture studies, if feasible.
  - Resistance and cross-resistance patterns for each drug in the combination regimen, as appropriate.
  - Anti-HBV activity data from clinical trials, for example, short-term monotherapy trials or dose-finding trials in combination with other antiviral drugs.
  - Phase 1 human safety data on each drug.
  - Dose selection rationale that considers potential for overlapping toxicities with the individual components should be outlined.
  - Drug-drug interaction data if the metabolism profiles suggest an interaction potential between drugs in the combination regimen needs to be evaluated.
  - Each of the investigational agents to be used in such an investigation of combination regimen should minimally have sufficient pre-clinical data and early clinical data supporting the rationale for studying the two investigational agents in combination.
- In regard to pharmacology and toxicology data, non-clinical combination toxicology studies of an investigation of a new agent, combined with an approved agent generally are not needed, unless pre-clinical or early clinical data for the new agents suggest a potential for serious synergistic toxicity with the approved therapeutic drug.
  - For clinical protocols assessing combination regimens with two or more investigational agents, we encourage early engagement with the agency for required combination toxicology studies and to discuss the duration of those studies.
  - International conference or harmonization, ICH M3(R2) guidance on nonclinical safety studies will be the generally applicable regulatory guidance, regarding animal combination toxicology.
- The following are a few general principles that might be helpful in the development of initial trials.

  - Starting with a small number of subjects, particularly first in human trials, for a product with a very high potential for an unpredictable acute immune mediated effects or off-target effects, it may be helpful to break the trial down into cohorts and to stagger enrollment into later cohorts until safety has been demonstrated in the earlier cohorts.
  - If a dose-escalation approach is to be used, the earliest cohort should receive the lowest doses. And safety should be demonstrated at the lower doses prior to dose escalation. Ideally, the lowest dose of study drug necessary to test the scientific hypotheses should be used.
  - Similarly, the duration of exposure to the study drug should be kept to the minimum necessary to test the scientific hypotheses. Based on drug's half-life, adequate duration of follow-up for safety needs to be outlined in the clinical protocol.
  - Early phase clinical trials should focus on the adult population without cirrhosis or with compensated liver disease.
  - For subjects enrolled in short-term trials, there should be a continued treatment plan to prevent hepatitis flares after discontinuation of investigational therapy.
- Efficacy endpoints for phase 3 trials.
  - One of the primary efficacy endpoints which is considered feasible for phase 3 registrational trials for novel therapies could be sustained virologic suppression of plasma, HBV DNA, and loss of hepatitis B surface antigen with or without seroconversion at the pre-specified time point after finite treatment duration.
  - Several exploratory or secondary endpoints should be evaluated as well.
  - Durability of treatment response needs to be demonstrated off treatment with longer follow-ups in a substantial proportion of trial subjects.
- Challenges in assessing clinical endpoints.
  - In terms of ALT normalization, a standardized definition of upper limit of normal is lacking and various labs have different values for their upper limits of normal. In addition, failure to normalize ALT may be due to other causes such as due to increasing prevalence of non-alcoholic fatty liver disease.
  - Obtaining histology data is not practical or a feasible endpoint in phase 3 trials.
  - Liver biopsy is not routinely obtained for clinical care as non-invasive assessments of liver fibrosis are increasingly being used.
  - Primary endpoints based on histologic parameters are not mandatory and efficacy in clinical trials could be demonstrated based on virologic and/or serologic parameters.
  - In terms of clinical outcomes such as decrease in cirrhosis, liver failure, hepatocellular carcinoma, or death, longer follow-up is needed to demonstrate an impact of novel therapies.
- Late phase trial design considerations.
  - Given the heterogeneity of the natural course of chronic hepatitis B, randomized trials are recommended to establish efficacy. A randomized active control design allows for a direct comparison of the efficacy as well as safety of

the study regimen. Trials can be designed with a superiority objective to demonstrate that the new product is superior to the control.

- Trial design may have a non-inferiority objective that the new product is unacceptably worse than the control.
- The new drug can be tested against placebo as an additional therapy to NUC regimen in patients who are virally suppressed on NUC regimen.
- We recommend sponsors discuss with the FDA regarding trials of an active control and choice of a study population before trial initiation. The active comparator in a phase 3 control trial should be an approved antiviral drug that reflects current practice at the time of trial initiation. Sponsors considering a non-inferiority trial design should discuss in advance their justification of the non-inferiority margin trial design and the data analysis plans in advance.
- Depending on product attributes, including resistance and toxicity profile, initial trials may be conducted in treatment-naïve hepatitis B antigen positive patients with active disease or hepatitis B eAg-positive or eAg-negative patients who are virally suppressed on NUCs.
- Initial trials may be considered in the adult population without cirrhosis or with compensated liver disease.
- Selection of the most appropriate population possible which would allow the scientific hypothesis of interest to be tested while maintaining an acceptable safety balance is encouraged.
- Trials should be designed to evaluate the impact of investigational therapy in patients with key disease characteristics.
- If multiple subpopulations are enrolled in the same trial, a stratification based on key variables should be considered.

- Safety evaluation
  - A thorough and comprehensive benefit/risk assessment ensures that the benefits outweigh the potential risk to the intended population. Benefit/risk assessment takes into consideration improved therapeutic effect of the new agent and demonstrated safety or tolerability profile in the context of underlying disease and current treatment options available.
  - Avoiding unreasonable and significant risk to clinical trial participants as well as patients is paramount.
  - One of the unique challenges with hepatitis B assessment is on-treatment hepatitis flares.
    - Pre-specified safety monitoring and assessment plan in clinical protocol is recommend.
    - Based upon safety profile in the earlier phase trials, a risk mitigation plan may be needed. Consideration should be given to incorporating stopping rules into the study protocol related to safety endpoint such as adverse events or lab abnormalities for individual subjects, cohorts, and for that trial itself.
- Resources for regulatory guidance

- Sponsors are encouraged to communicate with the FDA through the pre-IND consultation program.
- Guidance document for Co-development of Two or More New Investigational Drugs for Use in Combination may provide helpful general guidelines.
- FDA guidance for development of hepatitis B therapeutics is currently under work.

FDA Perspective on Hepatitis B Diagnostic Devices

Slides: FDA Perspective on HBV Diagnostic Devices

Presenter: Kathleen B. Whitaker, Division of Microbiology Devices, FDA

- Insight into what types of diagnostic devices are available, what types the FDA regulates, which ones they don't. For those of you interested in actually bringing a product to market, such as an HBV diagnostic device, we'll walk you through the steps that that entails.
- An RUO is when we're just coming up with a diagnostic device for a disease or for treatment that we want to look at during treatment of a disease. These are usually manufacturer-initiated studies, tests under development.
- Next, we have investigational use only in vitro diagnostic devices.
  - Prior to being able to send it to FDA or go to full commercial marketing, we want to just look and see how this actually performs in patients.
  - These results are generally not available to patients unless you have an investigational device exemption.
  - With an investigational device exemption, the patient can receive results from that particular device.
- We regulate devices for diagnosis, those that diagnose a disease, identify pathogens, confirm or rule out infection in symptomatic patients or those patients at risk for a particular infection.
  - We've never approved any screening assays. Those are all done under blood banking.
  - We also regulate epidemiological and surveillance devices and those devices which would give you a prognosis for the advancement of the disease or progression of the disease and predict which way the disease might progress or might not progress.
- Our approval is based on two things: safety of the device and efficacy.
  - Safety: Are there reasonable assurances based on valid scientific evidence that the benefit of this device outweighs any possible risk to health?
  - Effectiveness: Do we have reasonable assurance based again on scientific evidence that the device in the target population—and that's a critical point also—will provide clinically significant or clinically useful results?
- PMA-specific elements which are the manufacturing section.

  - A bioresearch monitoring group, that will go to either some of the clinical sites where the study was conducted or it could go to any of the sites where the samples were actually collected.
  - There's the possibility of a panel meeting. At this point, unless we have a particularly novel intended use for any new HBV assays or devices, we probably wouldn't do that.
  - In terms of post-approval, once it's been approved, there are annual reports to submit and supplements for any further design modifications.
- Analytical validation
  - Precision, accuracy, sensitivity, etc. These studies are fairly inclusive.
  - There's probably something else, but it all depends on the type of technology and the end-user for that device and also whether the device is quantitative or qualitative.
  - For both the analytical and clinical studies, we prefer to see real clinical samples where feasible unless it's a particularly rare analyte.
  - Retrospective samples are ok to use.
  - One of the most important things is comparison to clinical outcome.
- The clinical section of a PMA submission.
  - Study protocols including the IRB approval letters.
  - Informed consent from each one of the patients available.
  - The safety and effectiveness data.
  - A section on any type of adverse reactions and complications. Device failures.
  - What may be a bit surprising to some people is we want line data from every individual patient or subject in that trial.
  - A data analysis by the company submitting, although we'll often do our own analysis too.
  - Any other information from the clinical investigation that you may think is relevant.
- Labeling a device: under CFR section 809.10, we have all the necessary pieces that need to be actually in the labeling or the package insert. They need to have clear instructions for use. We have both the analytical and the clinical performance of the device in there and the performance in the intended use population.

Bringing Quantitative HBsAg to the US Provider, Drug Development and Patient Network

Slides: Quantitative Serum HBsAg Assay Validation for U.S. Patient Testing

Presenter: Robert G. Gish, Stanford University, HBV Foundation

- I'm going to present to you the technique of developing a quantitative sAg assay used by Quest. This is not FDA cleared. This is CLIA approved.
- I've talked about a lot of this, and basically my interpretation of quant sAg is I use it baseline in my patients. All my patients get a quant sAg. It helps me to determine their

current disease state or phase, and there's quite a bit of literature that's available for that.

  - I'll be following their quant sAg over time, just seeing if it looks like they're naturally clearing, or they've got a stable sAg.
  - Negative predictive value for SVR functional cures is very, very good in interferon treated patients.
  - A small number of patients on NUCs do clear sAg. They tend to start a little lower sAg, and then the sAg declines.

- Quantitative sAg development
  - Get commercially available plasma specimens with known sAg levels using WHO International standards in this sAg reference panel.
  - Have this QC sample system that's used, and they also had 15 low-level sAg positive samples that they bought from some commercial labs. Had serum samples with known positive/negative results as previously determined. And they had 40 blood donor sera who were screened by blood bank criteria.
  - Had in-house standards that were prepared and using purified sAg, known levels using ad and ay subtypes or serotypes.
  - These standards were tested in conjunction with other samples and used to construct this polynomial standard curve whereby unknown SCR values could be transformed. And the standards are known and had this range and the final analytical range of 0.05 which is consistent with the qualitative assay sensitivities up to 25,000 IU.
  - Test values were log-transformed again to be normalized and then the regression formula took place with an R^2 value of 0.98 with an acceptable slope. This met with acceptance criteria with a coefficient of variation R^2>0.9.
  - The specificity was at 100%.
- There's nothing in the US or the AASLD guidelines about how to utilize quant sAg. It hasn't quite met that threshold. Clinical practice guidelines from other organizations describe, including EASL, APASL, there's information in the WHO document, and then this NICE about how to use sAg in combination with other tests.
- Is there a market? Is there enough ROI to justify this? And I think the answer is yes already now. And with all the new drugs coming, looking at sAg reduction as an indication of early treatment response in phase 2 trials.
  - I think sAg clearance really is the goal for new drug development alone or in combination therapy.
  - I think off treatment sAg positivity, but DNA negativity off NUCs is not going to be enough I think to really move the field down the football field to provide much better care to our patients.
  - I really think our goal should be sustained sAg loss for the next wave of drugs.

Implications of HBsAg from Integrated DNA for Clinical Trial Design

Slides: Implications of Serum HBsAg from Integrated DNA for Clinical Trial Design

Presenter: Bruce D. Given, Arrowhead Pharmaceuticals

- I'm going to present a paper that was published in *Science Translational Medicine* a couple weeks ago.
- We got interested in doing an RNAi because, like everybody else, we thought the cccDNA was the be-all and end-all. The mini chromosome was kind of what mattered and what we cared about, and the way we've figured everything that the virus wants to do travels through mRNA. And we felt that if we could cut down—if we could basically severely repress the full transcriptome, that was going to challenge the virus in a way that had never really been done before, that the host really couldn't do, drugs certainly can't do.
    - We knew that the DNA could integrate into the host, but we weren't thinking of this as a source of mRNA as a transcriptive source. We reasoned if we could really have a big impact here, we could impact everything else that this virus wanted to do.
- People have known about integration for a long time. The belief system has been that the vast majority of it comes from double-stranded linear DNA, not from the relaxed circular DNA that most of us think of as the infectious DNA moiety and variants.
    - It turns out about 10% of circulating variants have this linear double-stranded DNA.
    - The interesting thing is when it actually does integrate into the host, you lose material at both ends. You uniformly lose the precore and core promoters, so you cannot make 3.5 kilobase RNA after integration.
    - Sometimes you lose the X promoter. Most of the time you don't, but even when the X promoter's there, usually you're losing material, so you're making a truncated X.
    - sAg is a different matter. The sAg promoter would be expected to be universally or near universally present. The full sAg open reading frame is expected to be present.
- As patients start to face immune pressure, actually the cccDNA burden goes way down, but the sAg tended to stay up. And that was in people's minds proof that cccDNA was still around and was still working. But this is probably what really happens. You get less cccDNA. You get less active cccDNA, and integration starts to become a much more important source and maybe even a dominant source of sAg.
- I want to point out a group of patients especially is every one of these patients here is DNA undetectable, core undetectable, eAg- of course. So eAg undetectable and HBV RNA undetectable. So there is no sign in the periphery that you could pick up from any of our current tests that there's any cccDNA activity here at all. Now, I'm not going to say there's not any. My point would be that whatever there is, it's so low that you can't pick it up in the periphery from any of our available tests today. And I would offer the possibility that all of this sAg here is coming off of integrated or almost all of it.

  - Integration's been shown to occur as early as acute infection. About 10% of variants have this double-stranded linear DNA instead of the RC DNA. This has largely been studied previously as a means of assessing clonality and also because of a lot of interesting in thinking this integration was driving HCC and that certainly there's a lot of evidence for that. This double-stranded linear DNA has been talked about as a result of sort of failed reverse transcription.
  - I think the important thing about here is that even with complete loss of cccDNA activity, if surface antigen persists, unless the host can control transcription itself or we're able to eliminate the cells that have active transcriptional forms—I'm sure there are many integrants that are not transcriptionally active. I'm certainly not implying that they all are. But unless you can do one or the other of these, I think that we're going to be dealing with this partial cure.
- We've looked at the inactive carrier state with a little bit of wonderment. My understanding is that while there's a lot less data, those patients who are able to maintain that state their risk for HCC and cirrhosis may not really be any different than functional cure. And it could be that that's what we're dealing with here in this inactive carrier state. It may just be a situation where all you're looking at is integrant-derived surface antigen and, in fact, cccDNA has been defeated.

HBV: Next Generation Sequencing, Data Analysis and Reporting

Slides: HBV Next Generation Sequencing

Presenter: Leen-Jan van Doorn, DDL Diagnostic Laboratory

- If you get the reads of a sequencer, what usually happens is that we first map them to a genotype or a subtype reference. What we do then is create a sample consensus and then we map again all the reads, and the second mapping is usually a lot more effective and efficient and more accurate than the first one.
  - If you have a sample sequence and you compare it to a certain reference, you can very easily determine the variants.
  - So on the one hand, we would like to have a good set of subtype-specific references to make optimal mapping. For hepatitis C, we have done this quite extensively.
    - Hepatitis B is slightly different. We have the different genotypes that are quite well defined. Subtypes, less well defined. And there is also not agreement on what to use as a universal reference to compare everything to, and that would actually be quite helpful.
    - So a simple proposal would be that maybe we can come up with a simple list of references we agree on, and we can use these for data analysis and reporting.
- I want to make the point it's a circular genome. So it's important how you annotate and where you start numbering. Historically, it has been done always on the EcoR1 site. It's tempting to do it where amplification starts because then you use the numbering of your amplicon. I think it would be a good decision to start off with the EcoR1.

- Third point—the final point—is the complete sample composition. However, this is not complete, and what we would argue for is to have a complete sample composition and not only include the information on the differences, but basically everything.
- In summary, if you do NGS sequencing from either the DNA or the RNA, that doesn't matter. A set of genotype and subtype references for mapping and reporting would be very helpful. We would propose to pick a general reference—probably this one, but that can be argued—as a universal reference. We clearly need more information on the subtyping and the naming of that as compared to hepatitis C. It would be good to use EcoR1 (TTC) as an annotation start site that the numbering is universal. And if you use complete sample composition in the databases instead of only listing reference-based variants, you can do multiple queries and have much more flexible reporting, and all the data become more or less comparable.

Panel Discussion

Members: Timothy Block, Hepatitis B Foundation; Carol Brosgart, University of California, San Francisco; Anuj Gaggar, Gilead Sciences, Inc.; Edward Gane, University of Auckland; Maureen Kamischke, Hepatitis B Foundation

- I'm going to tell you it's a little bit complicated for us community representatives. The virus is very complicated. So it's bringing it down to the patients is very key. There are populations that are impacted by this disease not only being concerned with having a life-threatening condition potentially or living with the threat of liver cancer or liver failure or cirrhosis in their future but also a disease that dictates their lives.
    - How will they be gainfully employed? Will they find partners and be able to marry, because they are discriminated against or left at the altar?
    - One particular consult that goes back to Vietnam every year so that she can fill her prescription. So I think that's just sinful that you can't afford your medication. She has to get all of her testing done there because it's easier. There are so many barriers.
    - When I think of what we need, I think it would be great if everything can be complete cure and cccDNA is eliminated and there's no transcription of sAg. But ultimately, to start with a functional cure is key so that people can live their lives. They need a finite solution to the problem. They can't be expected to be on long-term therapy for years for the rest of their lives.
- Another issue is being sAg+, it's better here in the US, of course, because here it's covered under the ADA. So there's some protection. Overseas, they flat-out can't work.
    - Many of them wish to work abroad in countries where they screen for hepatitis B. Their own countries won't even let them out. They're screened in-country before they—their applications never even make it out of country. So they can't support their families.
    - It's hard enough to find a decent mate rather than to worry about all of these little things like whether or not you're sAg+.

- You're damned if you, damned if you don't. You tell, don't tell. There's a vaccine, but when do you bring it up? Do you assume that everyone's been vaccinated?

- Anuj, let me go to you and ask when you see what Poonam presented which of course was started at the meeting just a year ago. What is your initial reaction to the outline of that in the virologic markers such as HBV DNA loss and surface antigen loss and then the additional exploratory markers that she mentioned?
    - I think maybe the most important presentation from the last several months because it really helps us understand the thought process. And like Poonam mentioned, it was really in line with the endpoints meeting. And I think that endpoints meeting took a lot of insight from the academics, industry, as well as the regulators. So I think it was really in line with how we've approached hepatitis B and we'll be looking forward to the document because I think it really gives the kind of guidance that we need. The types of markers and the definitions of cure I think also are in line with what we believe, and functional cure is still something we are striving to achieve for all the reasons that were just mentioned as well. And so, I think the hierarchy of what's the primary endpoints and exploratory markers to look at seems like a very good and rational approach and one that we are doing in our phase 2 studies.
- Tim, what do you think about the sort of new science? How do you think that affects how we look at surface antigen as an endpoint?
    - First, I'll say I'm very excited about the new science and really the work that Bruce Given reported is paradigm shifting in the way I believe the community will look and it has to adjust their thinking about control of hepatitis B. Since I used the word control and I have the mic and I'm at the HBV Forum, I want to propose that we change what we came up with at the endpoints conference that Anna Lok and Mark put together and we drop the term "cure." I think that's confusing and misleading. It's so qualified. And use the word "control" which you just used.
    - If [Bruce] is right, if they're right, it certainly changes the way we think about things. We have to think a lot more about what sAg on its own means. Is sAg a mediator of disease? Is it part of the pathology? Or is it just involved in tolerizing? Or is it an innocent bystander? Because if what he says is right, then NUCs alone have been paralyzing the cccDNA. That's the implication. So we've had the drug all along and we've been looking under the wrong lampshade. So these individuals are left with sAg that is coming strictly from integrated DNA and the cccDNA, even in the NUC treated eAg+ individuals.
    - When we're talking about clinical designs and populations to look at, obviously the groups that we're going to treat first will depend on the drugs and mechanisms of action. But as a rule, Dr. Mishra mentioned it might make sense or at least the opportunities will be different if we're treating people who currently fall outside the guidelines. And that's a population that won't be treated, that are largely in the naïve group. The immune-tolerant population, a group that is simply low risk for disease and not likely to be in your first line of thinking of treatment. But a group of people for whom it's very hard to

completely suppress virologically, rebound very quickly. But it will be a significant contribution, a major contribution, if you get people to the inactive state, off drug. And the immune-tolerant population may be the easiest way to look at that group because the rebounding—it's very hard to suppress them uniformly.

  - So you already have, I don't want to say FDA approved, but accepted endpoints. Virologically negative, viral load negative.
  - Rebound is very rapid once you go off drug. A new drug add-on if it suppresses that even by six months, you'll be able to get an endpoint.

- I want to put in a vote for take out the word "cure," put in the word "control," and consider the immune-tolerant population.
  - We don't want to be told there's a cure that isn't a cure. I'm saying it's misleading.
  - So I think this is something that we can come back to. I know from our experience in HIV cure research, we've had so many discussions about the implications of using the word "cure." In HIV, we sort of went to more of a virological suppression at a certain level over certain time or some people use the word "remission." But the word "cure" is a very aspirational and its sort of an emotional term as well maybe. So definitely, that's something we need to pay more attention to.
- Ed, welcome to the HBV Forum. what are your first thoughts, having heard what the panel has said and what you have heard and coming from your part of the world here? What would you change, if any, of what you've heard so far?
  - Listening to Maureen and having a similar discussion this morning on hepatitis C, I think what is a cure, I was asked what a cure means for that. And it really means that the person no longer has the infection, doesn't have the stigma, doesn't take tablets every day, and he/she and their family can get on with their lives knowing that they're going to survive and feel better and safer.
  - I do think we know that with model drugs in development that it is unlikely that any of them, any of the ones currently in clinical or pre-clinical will achieve that goal by itself. I do think it's important that we are able to duplicate what's happened in hep C over the last five years where the regulatory agencies relaxed and allowed agents in the early development to be combined. And I think we'd also like to look back a bit further and look at the way the HIV treatment was approached by different companies providing best-in-class drugs to achieve that goal.
- Carol, you could almost view that for a real cure it's almost like an intermediate step or something that would predict a real cure according to how Tim defines it. So what would be the best way to show the long-term clinical benefit of either a partial or functional cure? And should we even make a separation between those two terms?
  - the challenges that the clinician faces in encouraging that a patient should get on therapy because they want to prevent progression of disease, and depending on where someone is in the disease, it's sometimes easier for them

to understand that if they've already developed some degree of fibrosis or cirrhosis. So the therapy is going to bring them back from the edge.

- If they think they're fine and then they find this out incidentally and then as an evaluation is done they fit into treatment recommendations and the physician or the clinician is concerned about their progression of disease. And whether or not they have some advanced disease or they just meet treatment recommendations, you have to work with that patient around what it means to get on therapy, what the risks are if you're not able to be adherent to therapy. And just like in HIV, because if someone is in-adherent with therapy, you have risk of flare, but you also have the risk of the emergence of resistance.
- From the clinicians' standpoint, they would really like to be able to have a therapy where they're able to say that in X percent of patients we're able to achieve a sustained response and we can stop treatment. But then, there's always going to be the hook. Even if you get that, you're still going to be under surveillance because you still will have a risk of cancer. And that's hard for patients to even understand that if they're on chronic therapy, if they feel fine, and we've been able to suppress their viral load.
- I think, easier to get patients potentially onto therapy and to really stick with and complete therapy with this idea that it could be time-limited. It's going to be extremely difficult in something like chronic hepatitis B, as it is in HIV, where if people are feeling good, if we're going to make them feel really bad and the therapies, the once-daily NUCs, provided somebody doesn't have one of the infrequent side effects with them, are for the most part extremely well tolerated. So we're in a balance, and we're going to have to be very careful both because patients aren't going to like them even for a short period of time, and it's not going to be so short if there's going to be a lot of adverse experiences and if there's potentially dangerous ones like a flare and a flare that could result in decompensation.

- I wanted to ask the panel members what do they think about the proposed partial cure as an intermediate goal which was proposed during the last year's workshop, because I see more consensus towards functional cure and not too much towards partial cure.
  - Partial versus functional. I think there is more consensus towards functional cure like losing the surface antigen with or without seroconversion, but I don't see much consensus about partial cure where you can have patients have suppressed without or off therapy.
  - I think that I'm very enthusiastic about the idea of that increment. I think if you can get—kind of consistent with what you heard Maureen say. If you can get individuals to a point where they can be off-drug, off-therapy, and remain essentially in the same state they were when they were on NUCs, suppressed, virologically suppressed, off-drug indefinitely, that is a major advance. It's not a cure, and you've heard me express my discomfort with the terminology of cure.
  - The achievement and accomplishment of going off drug, I think that's a major contribution. So if I can take your new drug along with a NUC or without a NUC and then come off drug after a finite period of time and remain essentially in an inactive state, that is a major contribution. I don't think the community should

set the bar so high that everything's going to collapse and everyone's going to be disappointed when you don't achieve sAg suppression, S antibody recovery, particularly when it's not entirely clear what that means clinically.

- Obviously, this is very complicated and I absolutely agree that it's potentially an easier-to-achieve endpoint, one that has, at least from natural history, achieving that endpoint is associated with better outcomes for patients which is really, in the end, what we're trying to do. From a trial perspective, it's a slightly more complicated trial where we don't have predictors of who's going to have that state at the end. So that requires everyone stopping treatment in a trial to see where they end up, and that's obviously a different trial set-up but potentially need to consider the safety considerations in that kind of a trial versus one where the goal is surface antigen loss where you can monitor that on therapy and then discontinue treatment when you see that outcome. So I think that's one thing we have to think about on the trial end to make sure we can do that in a safe way to get there and not put patients at any risk with ALT flares or elevation. So I think that's one part that I need to think about more. But certainly, if we get that to that state and we have the data to suggest that for patients, that's a better outcome still in the long term. Yeah, that'd be a very reasonable outcome.
- The terms we use in cancer are remission, and then it's a remission over a period of time. So if someone had a sustained viral response off-therapy in terms of their HBV replication, their HBV DNA, and if that was coupled with sAg loss, if we had a name for that as being in remission.

- First of all, I wanted to make sure I didn't unintentionally mislead anybody here. So when I talked about those patients, they were all still getting entecavir. So I don't want anybody to think I was saying, "Hey, those patients were inactive carriers at that point," because they were still getting entecavir, because this really comes to Anuj's point. I think it'd be a reasonable thing in a controlled way to stop the entecavir in those patients and see what really happened, but it's not necessarily predictable that one or more or all of them might not actually see a recrudescence when the entecavir was stopped. So I just wanted to make sure I didn't leave anybody with an impression that we accomplished something we didn't. The second thing is I think that the current term for these patients, "inactive carrier," would also be a real problem, Maureen, I would think. No one wants to be a carrier, I don't think. I don't know if partial cure's the right term. I'm pretty sure "inactive carrier" is not the right term either. So it's not like we have one ready at hand to trade off for it.
  - And so this is why I'm thinking that it might be a good project between something like ICE-HBV and the Forum and the HBV Foundation to kind of have sort of a separate discussion on all of the terminology and proposals to at least destigmatize the terminology as much as possible and that might help the field.
- Just a quick comment and then a question actually for Dr. Mishra. A quick comment. I think saying "cure" when you're still at risk for hepatocellular carcinoma is irresponsible. And I actually believe that's also true in the hepatitis C space. We've cured infection, but these patients can have, albeit rarely, very aggressive HCC. So

what are you going to do when you look at that patient in the eye and say, "I told you you were cured, and now you have a life-threatening complication"?

  - I very much agree with what you're saying, and in fact, there are several people in our studies who were cured with hepatitis B NUC suppression who developed cancer. So they were cured, but they were then diagnosed with cancer. What about normalized? You're suggesting, Veronica, I think maybe a little task force to come up with some…

- [This] question relates to what needs to be done from single agents before you go into combination, and you put up a number of criteria, including MOA and in vitro testing, resistance, etc. You mentioned sort of phase 1B data on the monotherapy. Is that just for safety or are you expecting some degree of efficacy clinically before you go into combination?
  - So it's both. It's for safety as well as some kind of evidence of antiviral activity because that's how you get your information, how best to combine different drugs with different mechanism of action, so it's for both and, of course, PK data.
- So Dr. Mishra, did you differentiate between different classes of drugs, antivirals which may lead to resistance with monotherapy? Do you have a situation where you might limit the phase 1b studies too?
  - Yes, so that's why I said it will depend on the mechanism of the drug, the half-life and things like that. So it's very hard for me to say four weeks versus 12 weeks. It will depend what the drug's mechanism of action is. And when you propose, we can always help you figure out what will be the… And then, again, as I mention in the presentation as well, you have to have some plan for when these patients are off the monotherapy trial. What's your plan to keep them on therapy? Like will you continue a NUC therapy for them so that they don't react to it or there's no flare? All these will have to be outlined very well in your proposed clinical protocol, even if they're short-term trials or long-term trials.
- I'm Joan Block. So Carol, you were reading my mind exactly. I cannot believe the exact words. Because, as someone who lives with hepatitis B, I'm a very informed, educated person. I have really had a lot of trouble with the semantics of partial cure, functional cure, complete cure. The word "cure" for a patient has very significant meanings. And I don't think we should resort to using that word unless it is a cure. So I appreciate what Veronica was saying that maybe there should be a working group to really address that because that is completely misleading. Because part of semantics is using terms that people understand. The public is so well educated about the cancer terminology. Hepatitis B in and of itself is not the problem. The risk is that you can go on to liver cancer. So it is a cancer problem. So I don't think using the analogy cancer is a wrong thing. That is what we use to get people to get tested and into treatment. So I really like the idea of remission. Most patients understand that you get a disease, you get treated, you go into remission, and then at some point, you hope you get into care. And remission does remind the patient that they still have a risk. They still need to go into the doctor.
- I'm just thinking that it may also relate to coding, right? If you come back to have a visit and get screened for HCC, then how do you code that when the patient is technically,

supposedly cured, right? So I'm just thinking that that's another… I'll have one more question from Jean-Michel, and then I want to call on Jules and Eric to just give us a few seconds or minutes of your thoughts regarding the proposal that Leen-Jan made about the standardization. Is that something we should then take up for more discussion?

- It's more comment on the same topic. I completely agree with what was said. I hate "cure." It's misleading. Control or whatever we find. The problem is technical. I think the opportunity was missed because there was this EASL/AASLD conference where they say it was a consensus. I don't know where people were. I was not there actually. So my fault and others probably were not either. But a few people decided on this terminology, and it's been endorsed by the big associations. So I don't exactly know how we can move forward. The risk is that there will be a consensus on cure and another consensus of another group and another terminology and a third and a fourth and a fifth terminology. At the end, it will be very confusing. So maybe try to work with EASL/AASLD and try to do something like consensus meeting or whatever to correct it.
- I think it has to be official. It is very difficult to move backward after there was a statement, a paper in the two big journals. It's difficult. But it would be useful. So having everybody agreeing on something would be nice. And I'm afraid of 10 different terminologies from different groups, subgroups, subcommittees, etc.
- If we don't get the semantics right, but I think there's also another opportunity because at some point the division will be posting the guidance document for public comment. And that might be a place where with additional discussion that could be refined. And that's, of course, what will be used in the clinical trials and on the label eventually. I'd mentioned the Foundation and ICE-HBV, but certainly EASL and AASLD. And they are technically going to have their representatives on our steering committee, so we have that bridge built as well. And I think that's definitely we need to include and I think definitely bring in sort of the perspective of the meaning of cure and what that can entail.

- In HIV, we had many discussions about is it sort of incentivizing patients to participate in a trial if you have the word "cure." And so, in HIV, we don't have the word "cure" on any trial protocol anymore because no matter how you qualify it, when you see the word "cure," that's what you see. So I think we need to bring in additional people into that. But we're way behind the break, so Jules and Eric, who wants to go first about the proposal that we heard about NGS standardization?
  - I'm Eric Donaldson, a virology reviewer with the Division of Antiviral Products. And this is a conversation that we've been having back and forth, and it would be very helpful to have input from the rest of the scientific community regarding these issues with standardization for HBV sequences. So we currently don't have a recommended list of genotypes or subtypes. We basically leave that up to each sponsor. We kind of provide some guidance such as—well, I wouldn't call it specifically guidance, but advice that they should be representative of the genotype and the subtype of the geographic region that they're studying. They

should be described in the literature and justified in any study reports, things along those lines. But we're very interested in having more input.

- And it's a very focused question. So it shouldn't take three years' worth of working group discussion.

- So I don't have anything to add to Eric, but actually Bruce's presentation brought up a question I've asked a number of people and haven't really gotten a satisfactory answer to yet. Bruce, you mentioned that you had several individuals who were eAg- but were also negative for pre-genomic RNA, core rated antigen, etc., etc. And that had high levels of sAg. Do you know if anyone's actually looked to see…? So you might thing that most sAg would typically be associated with virus-type particles or virions. Do you know if anyone's looked in this case for these types of individuals if that sAg is sedimentable at a rate that's consistent with particles?
    - That's very interesting. No. I can tell you in these patients, no. I can't tell you if anyone else has done that under a similar circumstance. Part of what makes these patients interesting is it's not just eAg negativity and undetectable DNA and sAg. But for the first time also, we know that core-related antigen negative and RNA negative, so there's no marker that I'm aware of that anyone's talking about using that's not negative in these patients. So that makes them a different kind of patient than a patient that looks the same, but we don't know about RNA, we don't know about core-related antigen.

Diagnostics and Biomarkers Working Group Updates

Slides: Working Group Updates

Presenter: Pedro Goicochea, Forum for Collaborative research

- The working group mandate was to map how the markers that might needed for drug development and approval and review and discuss the regulatory path of the approval of such markers.
    - The activities of the working group have been working on during this year has been identifying the different HBV markers and what their regulatory approval is and also identifying to prioritize which markers have been approved either by the FDA or the European regulatory agencies and discuss which is the pathway that needs to be taken to get these approved.
- 141 assays were identified and imported into the fabulous tableau of public web-based software platform that allows us to do some searches on the different markers and search for them under their approval status, the type of marker, the company that produces marker, or the name of the assay.

Surrogate Endpoints Working Group Updates

Slides: Working Group Updates

Presenter: Marion Peters, University of California, San Francisco; Oliver Lenz, Janssen Pharmaceuticals

- Working group objectives: the first objective is to assess the available evidence between surrogate markers which can be measured in a clinical trial with a finite duration of a clinical trial and the evidence of the surrogate markers towards the long-term clinical outcome. The second point was to review, discuss, and formulate the evolving consensus on cure and their appropriate surrogate endpoints in HBV phase 2 and phase 3 clinical studies.
- Planned to do as a first step is to perform a systematic literature review and meta-analysis describing the link between surrogate endpoints and long-term clinical outcome. And we decided to start with functional cure, HBsAg seroclearance but also consider the partial cure.
    - There is a bit of debate of, in my opinion, needed if quantitative sAg would need to be added to the partial cure definition, and I think the partial cure is a very important endpoint given what Bruce has presented this morning, since patients who might have sAg only coming from integrated DNA might never reach a functional cure in a reasonable timeframe, but might be well off, off treatment.
    - Now what Ryan has done, he extracted data from more than 100 papers. He extracted that in a spreadsheet where he tried to collect all the relevant data and I think there are around 60 different data fields, which we are taking out of these papers. And there are more than 100 papers that represent 175,000 patients and more than 1 million person-years of follow-up.
    - As the next steps, which we want to do in terms of literature review, is to ensure that all relevant papers are included, and we had the working group call not too long ago where we asked the working group members to start looking at the papers which have been collected, the data which has been extracted to make sure that we capture all the important papers, all the relevant papers and include them. And we also invited them for comments if there is a feeling that a certain paper might not be the best one to include.
    - Additional preparation or check of the literature data needs to be done and then this can be further summarized and the meta-analysis could be started, and the meta-analysis, Bettina Hansen from Toronto and she has agreed to help.
    - Now, I also looked at the literature review, at the data which was coming out and it nicely confirms essentially what we expect—that there is a consistent trend for sAg loss, for example, being, as I stated, an improvement in long-term clinical outcome. However, the limitation of some of these studies, we don't reach statistical significance, for example, is that the patient numbers in some of these groups are small.
- We have been discussing that a bit further, and we felt we should be a bit ambitious and aim for something which would be a database, this really patient-level data, which would allow us to assess more systematically the link between the surrogate endpoint and long-term clinical outcome.
    - The database would be owned by the HBV Forum and physically located in Berkeley to make clear that it is not one stakeholder of the Forum would have privileged access to it.

- Bettina Hansen agreed also to play a very active role in that in terms of analysis.
- We realize that it is always a bit sensitive to provide your own data to a shared database and I know we have been also requested in some places to provide data and we have a lot of internal discussions: can we do that and how can we control that? And we are very aware of this challenge and we want to manage that by have clear rules, to have a scientific oversight committee that would be comprise representatives from the HBV Forum and all data contributors.
- We are currently working on a short concept paper outlining what we aim to do, working on a data collection template.
- It's really about sAg loss or other surrogate markers, like function, cure and long-term clinical outcome.
- We have started and we need to continue reach out to industry and academic partners with relevant data to assess the willingness to collaborate on this project.
    - So far, with the people we have talked to we have received quite positive feedback, with a clear question "Be more specific of what you want."
- I would like to take this opportunity to ask amongst this group is there is anyone in this room or who knows anyone outside of this room who has this type of data and might be interested to collaborate?
    - Veterans Administration System
        - I think they'll have some very interesting data, but it's going to be a bit different. I could be maybe for hypothesis generator and then testing more formally and other data sets, but I'm sure that they would have a lot of outcomes, but they wouldn't have the level of depth in the, I guess what you'd call it, characterization of the patients. But that's a good thought to keep in mind sort of as a complement to that.
    - In a totally separate project on fatty liver disease, we are actually in the process of putting together a database that consists of the placebo arms of completed studies to complement what we know about the natural history of NAFLD and NASH. So that might be something our industry members may also be willing to consider that as phase 2 and phase 3 trials report out and all of the analysis, etc., done, whether that would be something… We shouldn't just do it because we can do it, but would it really add some knowledge that would be useful to the field? It is talked about a lot to do placebo arm cohorts, but it hasn't been used that often and maybe just something to think about for the future in terms of just the placebo patients which are different from the real-world patients because they are still participating in the clinical trials.
- Also, for this database, the question will be would we also want data from new assays, like RNA correlated antigen in there? I realize the answer is, yes. But on the other hand, I realize that this new data is just generated and people

certainly don't want to share that because everyone wants to publish on it first, which is totally understood. In the long term, if we really get this database up and going, I would love to see that as a living database. So over years, data can be added which then can be re-analyzed, the link between surrogate marker and long-term outcome can be strengthened.

- We had contact with multiple potential collaborators on different aspects, and we are going to discuss if the efforts can be joined so that both data sets can be merged and could benefit the Forum and the whole field. We have also, as mentioned already, approached multiple industry partners, potential partners, to share patient level data.
- Professor Yang from Taiwan who owns the REVEAL data set and he constantly confirms that he is willing to share that data and he would be also willing to share his patient-level database.

- Given that diagnostic and biomarker working group will be coming to the surrogate endpoint working group and maybe just before moving on, I just want to make clear that all of the members of course are welcome to join this surrogate endpoint working group.
  - The question of course will be how are we going to set up the more extended group. That all needs to be discussed, and then the question is of course which questions should they tackle. Which topics could be included in the sub-groups?
    - To assess the value of novel markers, HBV RNA correlated antigen as clinical endpoints by monitoring the evolving fields, the literature coming out, the presentations being given, could be one example.
    - The other one would be the potential standardization of assays who measure novel biomarkers or novel markers. This could be virologic assay and the one which comes to mind of course first is HBV RNA assay. But it is not only restricted to virologic markers. Maybe you want to think a bit more about immunologic markers.
- Summary: The literature reviewed as mentioned is well underway. A lot of work has gone into it already. A lot of work still needs to be done, and we hope to start the meta-analysis soon that we can get some results together which can be hopefully shared at one of the next HBV Forum meetings. We are going to work towards a patient-level database by doing the next steps as outlined before. And then we have and will be exploring multiple collaborations and especially with the patient-level databases collaboration will be key. Because without people contributing data, we will have little to analyze. In addition, the standard scope of the working group is something we are going to be assessing, and again, we are looking for input from everyone on that. That brings me to the end of my presentation.
- Where do you see resistance sitting? As we start to get data and profile folks, where do we see resistance sitting, resistance testing, resistance profiling? Where do we see standardization of that sitting any of the working groups?
  - We know a fair amount about resistance in the NUC field. And some of these mechanisms of action will be different and there will be different things we

would have to look at. I think what Leen-Jan was proposing in terms of sequencing and what the reference standard is definitely speaks to the resistance. And I guess I would throw out to the group to what extent do we need to think about resistance beyond just how we sequence and how we frame and what reference we use in terms of moving forward? Obviously, for some immunotherapeutic agents it would be a different question than if it's direct-acting antivirals and stuff.

  - That's I think to be determined, but I think it's very relevant and, as you said, it nicely links to what Leen-Jan was presenting. I think there are enough topics to be worked through in a smaller group or in a wider group.

- Eric or Jules, in terms of resistance issues beyond that—we are already going to talk about the sequencing but anything else we should be thinking about in terms of virological changes and mutations and adaptations and all of that?
  - The phenotypic data would be nice to have I think across the different…and cross resistance data. We are seeing several companies having, for example, C-PAM inhibitors. And is there cross-resistance between those? I think that will be useful. I guess another point that I would make that we like to push is that when companies are doing their analysis for resistance, sometimes it is not clear from the genotyping whether the change is resistance associated and that is where the phenotypic data can be useful. But if you don't see a phenotype for something that occurs over and over again, we consider those still resistance associated.
- I would just warn about going down the immune rabbit hole. In HIV we could never get them to standardize immune assays despite 25 years of begging them to pick four or five assays that mattered and standardize them across the working groups. They simply couldn't do it. Every assay has a different meaning with every company that does it. If we are having trouble, struggling with viral markers, immune markers, is that x100? And I think it is a rabbit hole that I personally would recommend we avoid until it gets a little more clarity.

Treatment Combinations Working Group Updates

Slides: Working Group Updates

Presenter: Bruce D. Given, Arrowhead Pharmaceuticals

- Our aim was to facilitate the advancement of regulatory science for HBV combination therapy development to facilitate this open adaptive and iterative design for testing combinations similar to what was done for hepatitis C to such great effect.
  - We were looking to develop conceptual framework that would ensure that we were providing adequate safeguards for trial participants which is really at the core of what we are trying to think about here but still allow with this rapid testing and innovation regarding clinical trials of new combinations, because there is a general consensus I think in HBV that combination therapy is highly likely to be required here, as it has been in HIV and HCV.

- We also established this need to have a subgroup to approach this conundrum of a disease that very actively moves around transaminases, even in the absence of drug therapy. And then with the effective combinations, we expect that we will see a lot of flares, probably more than we historically saw with NUCs or interferon, perhaps much more. And nonetheless, we have all these new classes of drugs and all of these new small molecules and we will for sure see true, class DILI as well. And we may even see some pharmacological approaches that may produce their own effects on the liver that can produce transaminasemia.
    - Our initial co-chairs in the end were unable to really participate, so the subgroup is being reconstructed right now.
- The first deliverable was a white paper, suitable for publication, describing the working group recommendations in regard to doing this combination work.
    - We have authors from academia, FDA, EMA, and industry, and it has gone out to the full working group for review actually just in the last couple of days. This will of course carry the usual caveats for our regulatory colleagues that it represents their personal opinions and it does not set policy for FDA or EMA.
    - Principle number one was that there should be solid scientific rationale for pursuing the combination being proposed. It should make sense and generally this should be backed up by at least appropriate pre-clinical work. Although we recognize that especially with the loss of the chimpanzee as an HBV model, our HBV models are not great, especially for certain classes of drugs. But where it makes sense and is possible, we think that combination pre-clinical work should demonstrate that there is a reasonable expectation of value.
    - We of course believe that where multiple drugs are going to be combined, there should be a careful comparison of pre-clinical toxicology findings with these candidate drugs to be used in combination to determine if target organs overlap and also to really give strong consideration of conducting pilot combination toxicologic experiments. So this is one of these things where the default should be to do it. There should be pretty good reasons not to do it should be the general sort of overall perspective.
    - There should be review of clinical adverse events. As was mentioned before, these drugs should all have gone through phase 1A, 1B, maybe even 2A testing before we are thinking about putting them into the test kitchen for this sort of combinatorial kind of phase 2 work.
    - There should be some history then of the clinical adverse event history and pharmacologic effects. Again, the real goal here is looking for areas of overlapping toxicity or the potential for toxicity. This may influence the safety evaluations that should be required within the clinical trial. This may influence such elements such as starting doses, titration rules, stopping rules.
    - There needs to be a review of the routes of metabolism and clearance for the candidate drugs to assess potential for interactions that comes from that. And likewise, the effect of drugs on metabolic pathways and transporters. Again, just trying to make sure that people are extremely thoughtful and thorough in thinking of all the ways that risk could be introduced into combination therapy that could otherwise be missed. Once again, this may identify the need for

further pre-clinical or clinical assessments and maybe even pharmacokinetic interaction studies under some circumstances if it really was a significant area of concern.

- Determined handling of liver flares in all protocols. Again, as I said before, we believe that effective combinations can be expected or are likely to produce more frequent and possibly even more exaggerated flares than what we've experienced with NUCs and interferon. This would be especially complicated when one or more of the drugs in the combination actually has a toxicology signal in the liver in pre-clinical toxicology studies. So we may have the complicated situation if there is actually a tox signal and a high likelihood of producing response flares, if you will. And we believe that mechanisms should be included in trial procedures to be certain that flares get identified early and any emergent changes especially in liver function are identified early and are carefully considered of course.
- Any protocol-directed procedures, especially stopping rules I would say, need to be observed and this just has to be really emphasized. We believe, and this topic came up earlier today, that CHB patients with compensated cirrhosis should not be studied until we already have demonstrated in patients that are not cirrhotic and that we have a real efficacy, we've got acceptable safety, and we have progressed into phase 3 trials. Because the NUCs are very good drugs and very safe and well-tolerated, we think that the hurdle for going into vulnerable patient populations should be set relatively high in this disease.
- And patients with advanced cirrhosis should be excluded and Childs A/B decompensated cirrhosis should not be a clinical target until we've first demonstrated solid results in the less at-risk patients.
- Additional piece of advice, all-purpose, speak to the regulatory agencies because I think as Dr. Mishra said, to know one of these programs is to know one, to know one of these drugs, to know one of these combinations. Yeah, there is no one size fits all. We tried to write some general principles here, but in reality, that's no substitute for having real conversations that are in the context of the actual drugs that we are talking about combining.
- The submission of the position paper, we would hope, would be before the end of the year.

- I am very excited that we now have co-chairs for the DILI flare working group. Bob Fontana from Michigan and Maria Beumont-Mauviel from Janssen.
  - So the flare subgroup now it will all be about getting organized and operational. And I think the deliverable here initially, minimally, should include real operational recommendations for dealing with transaminase increases and other changes in liver function in the context of these HBV combination trials.
- Once we have the paper in and accepted, what we are thinking is that there are going to be more drugs progressing in the phase 2 trials. There are going to be combination therapy trials becoming more and more common. There is an opportunity to really monitor these circumstances, see what's going on, share and disseminate any relevant learnings, seek more opportunities to facilitate safe combination use as experience is

gained, and just try to facilitate rapid leaning, rapid dissemination, especially if there are any safety insights that we can gain.

- with the growing epidemic or pandemic of fatty liver disease and NASH, should we be thinking of, in addition to, not going into compensated or decompensated cirrhosis? Should we be evaluating the patients that come into these combination studies for whether or not they have NAFLD or NASH? Should they be excluded or should it just be noted? We may have complications in them that could potentially have us look at a regimen in an adverse way, when perhaps it really wasn't so.
    - This is clearly being an issue. It came up in the September joint meeting on endpoints that it was thought that we couldn't use ALT normalization anymore in our endpoints because the thinking was that the prevalence of abnormal ALT's because of NAFLD and NASH would be so high that we would be seroclearing patients, making them DNA-, and they would still have abnormal ALTs. So, this is clearly going to be a big issue and it needs to be thought through very carefully about what the approach should be. And I guess it's something more for you, Maria, that goes into the group. So, it's a triple problem now. Now it's DILI in the context of this epidemic of NAFLD and NASH and HBV, so it's more complicated, not less. And it's going to require real careful thinking about those issues. Most people have, I think, especially in early clinical trials have tended to sort of put a lid on how high the transaminases could be relative to even these exaggerated normal ranges that we use. So I think there is a general tendency in addition to—for instance, in our trials at least, we did FibroScans on everybody to try to limit the degree of fibrosis of the patients. And I think we did have an ALT limit as well just to avoid having livers that were too hot or maybe this potential for other things going on.
- How does the group feel on the spectrum of individuals who might enter a trial with a history of cirrhosis who don't meet current criteria? Are they a special group or they could be treated as individuals who don't have cirrhosis? If based on the FibroScan today they meet criteria, they're not cirrhotic or they don't have any clinical criteria, but they have a history. Are they a special group that we should treat differently or could we treat them like non-cirrhotic patients?
    - I don't have a clear answer for that. I don't know that that's going to be a very common patient that we're going to encounter, but maybe I'm wrong. Maybe we are going to encounter a lot of those patients. I guess I should give you the criteria might be individuals who are on NUC therapy for a long period of time. So there's some fibrosis regression. Let me qualify that. So they have a FibroScan of 8 or 9. Personally, I would not be prone off the top of my head to exclude a patient like that. But I would probably decide that in conjunction with our overall advisory board and the investigators in the trial. But my initial reaction, my knee-jerk reaction would not be to say exclude them.
    - The ALT issue is tricky actually. If you look at the phase 3 trials of NUCs, look at the baseline ALT levels, hep B patients generally have higher ALT levels than hep C patients and the average baseline ALT for most of the NUC phase 3 trials was run 120, 150. And if you use the central lab value of roughly 40 being ULN, that means patients with active disease typically come in three to five-fold

above normal. So that's what you're starting with. And it's kind of a tricky issue. Whereas with hep C, if you look at phase 3 trials, ALTs at baseline are typically around 70 or so. And yeah, of course, hep B patients are notoriously fluctuating as everyone here knows.

- Regarding that issue about cirrhosis regression. So we've got an ongoing study now where we've biopsied 19 patients who had initial biopsy years previously with cirrhosis. They've been on NUCs long term, and so these patients range from being on NUCs for anything up to 12 years to three years. So we found that most of these, the FibroScan scores are actually quite normal. They're below 7. But when you biopsy them, quite a lot of them still are cirrhotic. So it seems that the FibroScan scores are not reflective of the situation of fibrosis in this particular group of patients. But what is noticeable is that the fibro septa have grown smaller. So that is consistent with the FibroScan scores because it's less fibrosis. But they're still cirrhotic. So I think you need to be careful when we're using FibroScan to establish whether these patients are cirrhotic or not. It could be really underreporting cirrhosis in a lot of these patients.

Road Map of Research Priorities for HBV Cure

Slides: Road Map of Research Priorities for HBV Cure

Presenter: Tim Block, Baruch S. Blumberg Institute

- The Hepatitis B Foundation last year called together about 35 scientists and clinicians from academia and government organizations to put together what they thought would be the important research priorities that if followed would be most likely to lead to discoveries of hepatitis B cure, using the clinical definitions of a cure.
  - The results weren't enormously surprising, but they were binned into several different areas, ranging from virology to actually even getting to liver cancer management which is, of course, very important to those affected by hepatitis B.
- The general conclusions do focus on identifying cccDNA, but actually, there are many roads to the elimination of cccDNA that are both obviously virological and also immunological.
  - We've put this all together in a publication that's coming out next month in Hepatology.
- So we actually bothered to say if we've identified these research priorities and identified these research projects that have worked on we think are most likely to lead to cure discoveries, what would be the cost of this cure?
  - We put this together and put them into specific projects and worked with appropriations members from the—a little US-centric—US House Appropriations and House Senate Appropriations Committee and asked them to help us identify what would it cost if this was expressed into funding projects at the NIH. And we actually have put a price tag on it of an additional 45 to 46 million dollars a year of research at the NIH.

International Coalition to Eliminate Hepatitis B (ICE-HBV) Scientific Strategy Consultation

Slides: International Coalition to Eliminate HBV

Presenter: Peter Revill, Doherty Institute

- The aim of ICE-HBV is a safe, affordable, scalable, and effective cure. Our vision is to be an international, independent, research-based and, importantly, patient-centered forum.
    - The genesis of this, the basis for the idea came from the International AIDS Society cure initiative for HIV where they set up international working groups in virology, immunology, innovative tools, and clinical studies, and that's been going since 2010 and it's directed at HIV cure research and advocated for funding and been very, very successful.
    - We don't have a "clinical studies" working group because that's what the Forum's doing. So we're working with the Forum.
    - Our governing board at the moment, our honorary president is Frank Chisari. I'm the current chair. Fabien Zoulim is the co-chair, and the other members are Massimo Levrero, Stephen Locarnini, Jake Liang, and John Tavis.
    - The stakeholders working group, importantly, is chaired by Veronica Miller, Ulla Protzer, and Tim Block.
    - Our senior strategic advisors at the moment: Professor Ray Schinazi and Professor Christian Brechot.
- Our working groups. We have virology headed by Maura Dandri and Haitao Guo. We have immunology headed by Adam Gehring and Robert Thimme. Our clinical study co-chairs as I've mentioned before and our innovative tools group, headed by Jianming Hu and Fengmin Lu. We have broad continental, different continent representation. We have people from Africa in these working groups and throughout Asia, through Oceania, through the United States, and through Europe. We're not represented too well by Latin America. We're very aware of that. We're going to address that.
- Current projects:
    - We're producing a joint position paper on what will be needed to achieve HBV elimination.
        - So, our working groups through engaging the basic scientists, the clinicians, public health, research organizations, and industry and patient forums, that's how they came up with this paper.
    - The working groups are working on a cccDNA assay standardization.
    - We started up a mathematical modeling program with Stanford University
        - we think there's a real need for point-of-care diagnostic assays, particularly in lower and middle-income countries and more harmonization studies.
- Started to prioritize the main areas of HBV cure research in virology, immunology, and innovative tools.
    - Immunology

        - The main priorities, the five leading priorities come up by this leading immunology group to develop new methods for ex vivo analysis of HBV specific immunity in the blood and in the liver to better correlate a HBV specific immunity for the stage of disease and response to therapy. Next, to determine the relative contribution of different mechanism of T cell exhaustion. The extent to which HBV specific immunity can be restored and how much restoration is required for HBV cure. Analyze the role of B cells. B cells is an understudied area in HBV specific immunity. A clearer understanding of the quantity of infected hepatocytes. Relative contribution of the cytolytic and non-cytolytic clearance induced by the immune response and immune therapies in the liver. We need standardization of immune monitoring in clinical trials that needs to be tailored to the drug's mechanism of action with appropriate timing and intrahepatic sampling.
    - Virology
        - Define the mechanisms determining HBV infection establishment: from cell entry to cccDNA formation. Develop standardized methods to study mechanisms of cccDNA homeostasis and processes affecting its stability and activity. Understand the role of the circulating viral markers to predict HBV functional cure, serum RNA and what have you. Understand the role of DNA integration in carcinogenesis and in HBsAg production.
    - Tools group
        - Develop efficient and convenient in vitro infection assays. Develop new research assays. Develop convenient and reliable markers for cccDNA and point-of-care diagnostics as I've said for hepatitis B, particularly in lower and middle-income countries, and develop new methodologies for cccDNA studies.
- Point one for the immunology group: define biomarkers that identify patients who can safely stop antiviral therapy and reflect intrahepatic immunity in the peripheral blood. CD8+. Determine the relative contribution of the different mechanisms as I said to T cell exhaustion. So CD8+ T cell exhaustion is linked to expression of inhibitory receptors, dominantly PD1, and mitochondrial dysfunction. But T cell failure, learn more about the contribution of the different mechanisms, whether T cell restoration is possible, and if so, how much restoration is necessary for HBV control. And then standardization of immune monitoring in clinical trials. This group has suggested that we need access to peptide libraries, for example. There needs to be consensus on flow cytometry panels for immuno-profiling, and there needs to be general standardized protocols for functional analysis of immune cells, be they T cells, B cells, monocytes, NKs. These should be made available to the HBV community potentially through ICE.
- In terms of virology, define the mechanisms determining HBV establishment from cell entry to cccDNA formation. So what are the processes contributing to cellular uptake of HBV? The conversion of rcDNA to that episomal cccDNA. It's still a lot of a black hole there. And the association with histones. Terrific talk from Fabien Zoulim yesterday or

the day before on the association of histones, and histone proteins to build a minichromosome. But there's so much more we need to know. And what are the early virological events in initiating cccDNA transcription and the role of possible host restriction factors? Develop standardized methods to study mechanisms of cccDNA. So collaborative research efforts are needed to establish standardized methods for specific cccDNA quantification in the liver and the tissue and in cell lysates. Now, this is a current working project of ICE-HBV. We need improved ChIP assays for chromatin analysis. The role of HBc and HBx in cccDNA activity and in the maintenance of cccDNA. And what's the impact of polymerase inhibitors on cccDNA half-life?

- In terms of tools, we need to develop convenient and efficient in vitro systems. So there's a lot of work now on iPS, on induced pluripotent stem cells. We need to coordinate this work I think in different labs because they're very, very difficult to work with. We need to potentially transplant primary human hepatocytes and human HLCs into the liver of mice and then getting them back out again. And that might be much more efficient than trying to extract and grow primary human hepatocytes in isolation. These models need more work. We need to develop convenient in vivo model systems. So we need a better mouse model. We need an immunocompetent mouse model. We need to look at other models, so non-human. I've got "primate" here in quotation marks because the Tupaia is apparently more closely related to primates than it is to rodents. It's quite interesting. But the Tupaia model potentially needs to be reinvestigated. we need to develop new research assays. So in situ, single-cell, single-molecule, live-cell assays to elucidate the biogenesis and stability of cccDNA and to be able to track it, to localize it, track it in the cell. We need to develop convenient and reliable methods to detect the markers for cccDNA, be they the empty virions, the core-related antigen, the serum HBV RNA. We need to develop new methodologies for cccDNA studies. So we need to harmonize the different methodologies that are used to quantify cccDNA. I'll talk about this project in a minute. We need to develop new strategies to improve the specificity and sensitivity of cccDNA measurements because there's only one or two cells.
- So I think what we can do as ICE, and this is where I'd love feedback from people in this room, is what's the next thing that we can do in terms of these standardization projects.
    - We need to look really carefully at these serum markers and how real they are as markers of cccDNA expression. We need to perhaps standardize ChIP assays. What's the role of x and core in cccDNA activity and maintenance? The cell culture models. These could all be standardized across different labs across the globe, including the new in vivo models and all the other things I talked about. Through ICE, I think there's a real opportunity to work together and through the HBV Forum to make this happen.
- In two years' time, we're holding the International HBV Meeting in Australia. I would like everybody in this room to come.

Discussion

Presenter: Peter Revill, Doherty Institute; Tim Block, Baruch S. Blumberg Institute

- Uri Lopatin with Assembly Biosciences. Peter, question to you about ICE and some of the biomarkers you're looking at. Something that we've discussed a lot today and over the course of AASLD and other meetings has been the use of sAg, whether qualitative or quantitative, but none of us actually know what we're saying when we talk about changes in sAg because sAg is a good mix of all sorts of different moieties in the serum. Are you looking in ICE at any way to differentiate what the sAg is in patients that are on different states?
    - No, but we need to. I really think it's critical. And distinguishing sAg that comes from integrated as opposed to sAg that comes from non-integrated. I probably should have that top of the list to be honest.
    - So just by an antibody test do you imagine that you could differentiate them? Not integrated versus sub viral particle. But that's what I think. But you can distinguish them based on RNA, on the transcripts. But the transcripts, by and large, you could discriminate those that come from integrants versus cccDNA in theory.
    - It might be a digital PCR approach, but not many people have digital PCR.
- There was a really nice presentation yesterday on persisting epigenetic modulations after cures in hep C. And they were not totally able to link it to late-developing HCCs, but it was starting to sort of look like that because a lot of the modulations did relate to gross-related genes in the cells. So the question is this part of the mystery of long-developing HCC years after people are "inactive or cured." The question for these folks, especially Peter with a very wide reach on all the research, is anybody looking at persisting genetic and epigenetic modulations after patients achieve inactive carriage or durable sustained post-treatment responses?
    - So you're talking about the genetic changes, epigenetic and genetic changes that occur as a function of chronic infection in the somatic cells.
    - Yeah, somatic cells. So I wouldn't say there's an overwhelming amount of work on it, but there's a body of work that's going on characterizing that. The NCI has a cancer atlas, and they're now just beginning to address the epigenetic changes. They created an atlas of the somatic cell genetic changes.
    - But if your point is that that's a priority to be built into the ICE agenda, I agree. It's certainly not comprehensive work that's done, but there is some work being done.
- This is a question both to Peter and to Tim. With the global involvement through ICE and then through the Hepatitis B Foundation, given how little money is invested at a federal level in the United States at NIH or through the grants that are available to young scientists or established scientists, either in HBV, HBV cure efforts, or in hepatocellular carcinoma and the rising rates of that, within ICE is there a plan to have a political advocacy arm around funding from all of these national sources so that we can up the amount of money that each of the countries and each of the regions is putting into this effort? And then along with that, working with some of the foundations and whether it's the Gates Foundation or the Bloomberg Foundation, where there's big

money, to be going after them too and not just governmental. But that's more of a political action funding group.

- It is important, and in fact, the Gates Foundation Beijing are a part of our stakeholders group. We haven't got Bill Gates, but we've got Beijing as a start. And it's critical. I saw a statistic. There was a lovely paper in *PLOS* a couple of weeks ago that HBV should be treated as a neglected tropical disease.
- Another statistic I saw the other day is that 53 million dollars per year was spent on hepatitis B funding in the UK and US combined. And at the same time, for that same period, it was 3 billion in HIV research. So that's kind of what we're up against. That's been the historical situation that we need to change. And so, we think with our position paper and Tim's roadmap, they're going to be terrific documents that we can advocate. And you've already been to Capitol Hill and it looks like you're hopefully going to have success. But we need these sorts of flagpoles in the sand that we can hold.
- We are calling for an international fund. We're proposing this, and I was talking to Peter about this this morning about ICE-HBV taking on an important role in this. We want to structure it. We're beginning to talk to some of the international agencies. We spoke to Nick Walsh about putting this to the WHO. But it's something that ICE-HBV can take an important role, if not a lead, on calling for an international fund that would collect funds from across the world, from different government and non-governmental organizations to put into the fund which would be distributed for research.
- There should be an aggressive movement put forth internationally to raise money. And yes, the Hepatitis B Foundation in terms of its advocacy is really largely a US-centric organization. So a bunch of us gathered together in a coalition through ICE, through the WHO, and some other organizations makes a lot of sense.
- But we're still battling that perception that hep B's okay because there's a vaccine.

- How would you like to receive feedback?
  - We don't want to reinvent the wheel. That's why we haven't started an industry group, liaising with industry and regulatory bodies through the Forum. So I think feedback perhaps through Veronica.