

## **Meeting Summary**

### **The Liver Forum 1**

Thursday Nov 6, 2014

Boston, MA

#### **Session 1: Introductions and Project Overview**

- Welcome & Introductions
- Governance & Forum Process
- Goals & Objectives

Moderators: Gary Burgess, Veronica Miller, and Arun Sanyal

- Veronica Miller welcomed everyone to this kick-off meeting of the Liver Forum.
- Gary Burgess and Arun Sanyal, co-chairs of the steering committee, noted that there are persistent unmet needs in the clinical care of non-alcoholic steatohepatitis (NASH) and progressive liver fibrosis and acknowledged the number of meeting participants as a reflection of the growing interest by industry, regulatory authorities, and the academic community to address these unmet needs.
- This project builds on the September 2013 workshop held jointly by the U.S. Food and Drug Administration (FDA) and the American Association for the Study of Liver Disease (AASLD). It will be an ongoing collaborative effort to advance research and development for therapeutics and biomarkers to treat liver diseases.

Veronica Miller presented an overview and history of the Forum.

- The Forum is a public-private partnership formed in 1996 to facilitate HIV drug development. It included representatives from government agencies, industry, researchers and clinicians, insurers, foundations and the patient advocacy community.
- The model was applied to hepatitis C virus (HCV) drug development in 2006, and is now being applied to two new disease areas, cytomegalovirus (CMV) in transplantation patients, and liver disease. For 2014 and beyond, the mission of the Forum is “Facilitating Collaborative Research in Drug Development and Health Policy”.
- The Forum provides a neutral and independent space for stakeholder engagement and science-based discussions. The goal is to achieve an evolving consensus when possible, through ongoing collaboration and collective ownership by Forum members.
- The Liver Forum is jointly led by the Forum, AASLD, and the European Association for the Study of the Liver (EASL). The full Liver Forum will meet twice yearly in association with the Society conferences, with ongoing activity by working groups in the intervening months.
- Sponsorship of Forum activities is broad-based.
  - The Forum receives contributions through UC Berkeley Foundation.
  - Forum projects are self-funded, i.e. Liver Forum activities are funded by liver-specific funds. Forum staff is pursuing a broad funding strategy, including funds from federal, foundations/trusts, societies, and industry.
  - Industry membership is open to scientific experts from companies with commitment to disease area, and companies provide voluntary contributions.

- All stakeholder groups represented on Steering Committee, which is co-chaired by one academic and one industry representative. Industry participation on steering committee will be rotated after the first year.
- The objectives of today's meeting are to:
  - Launch the Liver Forum, meet players, and understand process and governance
  - Understand the regulatory perspectives from EMA and FDA
  - Identify two or three high-priority areas for setting up working groups, which will delve into more scientific detail. The working groups will report back at the next project meeting, which will be held in conjunction with the EASL International Liver Congress in April 2015.

## **Session 2: Regulatory Considerations**

Moderators: Scott Friedman and Detlef Schuppan

Presenters: Elmer Schabel (EMA/BfArM) and Chris Leptak (FDA/CDER)

### Elmer Schabel (EMA/BfArM) (phone)

Elmer Schabel is a member of the European Medicines Agency (EMA) and BfArM, the German regulatory agency, as well as EMA's Scientific Advice Working Party (SAWP) and chair of the Gastroenterology Drafting group (see below).

#### “European Regulatory Network and the Liver Forum”

- EMA is the “networking agency” for 44 national medical regulatory agencies and includes 3500 national experts. Within EMA, the Committee for Human Medicinal Products (CHMP) is responsible for the Agency's opinions on human medicines. The Scientific Advice Working Party (SAWP) is appointed by CHMP to facilitate R&D and patient access to medicines by giving advice to companies during drug development. The Gastroenterology Drafting group is appointed by CHMP to prepare scientific guidelines for drug development on gastroenterology and hepatology.
- The SAWP gives advice to companies at any stage of development. Advice is not legally binding and is intended to avoid major objections regarding test design that would be raised during the evaluation of a marketing authorization application (MAA).
- Biomarker qualification is a special procedure within the SAWP process, and falls under “qualification of novel methodologies for medicine development.” SAWP reviews data provided and makes recommendations to CHMP. After a period of public consultation with the scientific community, CHMP can issue a “qualification opinion” on the acceptability of a novel biomarker. If data is not yet available, CHMP can provide confidential “qualification advice” on biomarker development.
- To date, EMA has little regulatory experience with NASH or non-alcoholic fatty liver disease (NAFLD). There have been no MAAs, and three compounds have been presented for scientific advice, including the now abandoned rimonabant. No regulatory guidance documents are available.
  - In terms of scientific advice discussions, NASH was accepted as a valid indication and discussions included the design and duration of phase 2 and 3 studies. The hard clinical endpoint of liver transplant was considered not feasible for phase 3 trials, so histology would be accepted but should be based on fibrosis

development. Finally, on the discussion included how to deal with standard non-pharmacological treatment (e.g., weight reduction), especially when a compound (e.g., rimanabant) also has effects on body weight, which in turn affects liver outcomes.

Discussion followed the presentation.

- What is the most effective way to facilitate communication between FDA and EMA, in an effort to increase harmonization?
  - Companies can initiate interaction with both FDA and EMA on their drug development plan in a similar timeframe, ideally early before too many decisions are fixed.
  - There are formal mechanisms for the agencies to communicate and harmonize processes. For example, for biomarker development, FDA, EMA and other global regulatory bodies have common templates and common formats for data submission.
  - It is envisioned that the Liver Forum will provide an informal structure for flexible interactions between the regulatory agencies. Today's meeting provides an opportunity for the agencies to begin a dialogue on approaches to future NASH guidance. Additionally, Liver Forum working groups can identify and promote the generation of new data to overcome scientific gaps, evidence that would be available and useful to multiple regulatory agencies.

#### Chris Leptak FDA/CDER (phone)

Chris Leptak is the Biomarker and Companion Diagnostic Lead in the Center for Drug Evaluation and Research (CDER) Office of New Drugs (OND)

“Biomarker utility and acceptance in drug development and clinical trials – an FDA regulatory perspective”

- FDA uses the biomarker definition developed by a 2001 National Institutes of Health (NIH) Consensus Group: a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. Note that biomarkers that are best suited for use in drug development are not necessarily ideal for use in treatment decisions.
- Types of biomarkers include disease-specific (e.g., diagnostic and prognostic biomarkers) and therapy-specific (e.g., predictive, pharmacodynamic, and efficacy response surrogate biomarkers).
- FDA evaluates biomarkers through either drug-specific applications or a formal qualification process (reference [guidance](#): Qualification Process for Drug Development Tools). Biomarkers are qualified within a stated context of use, which may include criteria for how samples are obtained, and a specific range of animal species, clinical disorders, or drug classes. After qualification, the results of patient assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making. Context of use can be expanded in the future with additional information. Most development programs to date have focused on efficacy surrogacy endpoints, which require more data, but it's important to note that biomarkers can be qualified for different purposes, including enrichment of trials.

- Emerging best practices include control for variability (e.g., sample collection and storage, analytical methods) and bias. Banked samples are acceptable but testing should be confirmed/supplemented with fresh samples when possible. Note that for imaging biomarkers, it's important to talk to FDA early about the specific molecule because the molecule (e.g., a radiolabeled marker) could be considered an imaging drug and require an IND.
- Other opportunities exist for stakeholder groups and consortia like the Liver Forum to engage with FDA on biomarker development, including a Critical Path Innovation Meeting. Through a new pilot program, FDA can also publish a Letter of Support, which publicly describes their thoughts on the potential value of specific biomarkers, to help support biomarker development, encourage data sharing and stimulate additional studies.

A discussion session followed the two presentations.

- What is the best way and timing to approach validation process for companion diagnostics? For example, with HCV drug development, single nucleotide polymorphism (SNP) was a commonly used but unvalidated method, resulting in uncertainty about how FDA would consider use of the method.
  - If a drug developer doesn't have internal diagnostic capability within the company, it is important to seek a diagnostic partner as soon as a device is considered to be helpful for patient selection, dosing, monitoring, etc. Studies can use a commercially available test, homegrown test, or clinical trial assay, but device performance characteristics should be well validated before phase 3 of therapy studies, otherwise treatment data may not be interpretable.
  - CDER and CDRH will work with companies to help develop device performance characteristics in an iterative process similar to drug development. CDRH uses a pre-submission process to engage with diagnostic developers. If the diagnostic meets the threshold of essential for safe and effective use of product, then it will be designated a companion diagnostic. For most programs, the threshold definition is not met, but there is still benefit from studying the drug and device together. In cancer and antivirals, CDER and CDRH have good recent history of joint meetings with drug and diagnostic groups.
- Standardization is critical, from disease definition and target patient identification to validation of biomarkers for treatment outcomes.
  - Initially, the community should work to agree on the definition and key characteristics of fibrosis, including methods for measuring the key characteristics. The pulmonary community is undergoing a similar process on the definition of lung fibrosis, which includes collagen deposition, cross-linking, stiffness, and other characteristics.
  - Identification and validation of biomarkers that reliably help identify high-risk patients and diagnose disease should be high priority, as heterogeneity of target populations is currently a big challenge for NASH trials.
  - Finally, validation of prognostic biomarkers that correlate with disease outcomes should be pursued.

- There are clear challenges with variability of quality of liver biopsy and histology, the current gold standard for comparison of new biomarkers. In the short-term, it will be important to develop quality standards for use of biopsy as a control. Future methodology that is mechanism-based, such as all-organ quantitative imaging of fibrosis or fibrogenesis, may be able to replace biopsy as a gold standard for serological markers.
- To contribute to biomarker validation, companies can include panels of potential fibrosis markers in their clinical trials (phase 2a, b, 3). In order for data to be comparable across different studies, and for placebo arms to be pooled for validation efforts, it is important to standardize data collection, and the Liver Forum can lead that process.
  - For biomarker qualification, FDA encourages using similar standards as drug development. Good resources to begin with include FDA standard on clinical imaging endpoints and the Foundation for the NIH Biomarkers Consortium.
- A mechanism for pooling data on genomics and expression arrays will also be important for identifying biomarkers for further validation.

### Session 3A: Identifying Gaps and Barriers

- Natural History of Disease
- Biomarkers for Disease Staging and Entry Criteria
- Biomarkers and Diagnostics for Study Endpoints
- Definition of Response in Patients in Different Disease States

Moderators: Gary Burgess and Laurent Castera

Discussants: Stephen Harrison, Joanne Imperial, David Shapiro, Mani Subramanian, and Peter Traber

- A forthcoming systematic analysis in *Clinical Gastroenterology and Hepatology* reviewed 11 natural history studies, covering 440 patients and 2100 years of follow-up.
  - Patients with NAFL and no fibrosis developed fibrosis progression at a rate of one stage every 14 years. Patients with NASH and particularly those with fibrosis developed progression at a rate of one stage every 7 years.
  - A group of rapid fibrosis progressors advanced from stage 0 to 3-4 over 5.9 years and comprises 10% of patients, but it's unclear how to identify this group.
    - Data from the NASH Clinical Research Network (CRN) suggests that some characteristics of rapid progressors may be identified from a group that has F2 and less advanced fibrosis. Patients with full-blown metabolic syndrome are also likely to progress faster.
- Two approaches were discussed to improve natural history information.
  - One approach is to establish an international biobank/database for contribution of samples and data (e.g., plasma, histology). There are many different therapeutic approaches in this disease area and thus interest in different biomarkers. It will be critical for working groups to identify characteristics such as patient entry criteria (e.g., abnormal liver test, steatosis on ultrasound, NASH on liver biopsy, combinations) and length of follow-up.
    - To correlate with clinical outcomes in liver disease, cancer, cardiovascular, and other areas, histology and other imaging modalities (e.g., MRE, MRI) will be needed. It is also important to think about

collecting additional data that reflects the underlying heterogeneity of patients, e.g., related to obesity, insulin resistance, etc.

- It could be possible to examine RNA expression in tissue samples, identify upregulated genes in rapid fibrosis progressors, and develop a serum blood test.
- A second approach is to analyze historic biopsy samples using current histological criteria for NASH, examine liver-related outcomes and mortality, and determine the long-term predictive value of histological lesions for outcomes. Similar work has been done on small cohorts, but could be expanded with the existence of many old biopsy samples and data that includes long follow-up times.
- Additional questions to consider:
  - What interval change is important for these markers, e.g., 5%, 10%, 20%, p-value?
  - What is the importance of variability in alcohol consumption? Should there be stricter standards on level of alcohol consumption?
- A challenge for disease staging biomarkers is that even when biomarkers are carefully selected based on available information from animal, diagnostic clinical studies, and cross-sectional studies, often clinical trials will encounter strong variability in placebo patients.
  - The role of hepatic venous pressure gradient (HVPG) and collagen proportionate area (CPA) as potential regulatory surrogate biomarkers should be investigated further
- There was much discussion about how to move away from liver biopsy and towards function, including what is meant by function. There was some disagreement about what are the most important clinical outcomes that eventually lead to death in this disease area, but there was general agreement about a need to consider a global assessment of liver organ physiology and function. The goal is to identify a series of function tests and biomarkers that will provide an assessment of the risk of developing complications such as portal hypertension, shunting, variceal bleeding, ascites, etc. Such global liver function/physiology is likely at the heart of reversibility and should be carefully defined and examined.
- There is increasing evidence of the prognostic value of liver stiffness with fibrosis and HVPG. There is additional data in other liver diseases (viral hepatitis and primary sclerosing cholangitis (PSC)) showing correlation with hard outcomes such as hepatocellular carcinoma (HCC), complications, and death.

### **Session 3B: Identifying Opportunities for Collaboration**

Moderators: Scott Friedman and Arun Sanyal

Discussants: Jeff Bornstein, Sophie Megnien, Andrew Muir, Jerry Stern, and Eric White

Discussion from the previous sessions surfaced three distinct opportunities for collaboration:

- 1) Establishment of a biorepository
- 2) Development of a clinical registry for natural history studies
- 3) Standardization of data and information to enable comparison across trials

The recent development of a biorepository for idiopathic pulmonary fibrosis (IPF) (ref) provides an opportunity to examine challenges:

- Intellectual property issues can arise with collecting samples from patients who may have received a proprietary compound, but it is easier to gain agreement on use of samples from placebo arms.
- Informed consent is a challenge because patients have not previously given consent for samples to be shared.
- It is critical to gain agreement on sample types, collection methodology, storage conditions and length of time, and clinical information.
  - Could combine repository with registry to ensure clinical information is available.
- It is also critical to agree on the allocation and use of samples. The IPF repository will use a “study section” composed of repository contributors to examine proposals for scientific rationale. There may be IP concerns over disclosing study plans in proposals, but concerns can be alleviated by a level of mutual trust and an agreement that study results are owned by those conducting the studies.
- Many academic groups, including the NASH CRN, already have biorepositories that may be leveraged. It is difficult to get NIH funding for transcriptomics studies and other analysis of biorepository samples, but FNIH may be a potential source for funding.

A clinical registry can be established, similar to those established in PSC and primary biliary cirrhosis (PBC) to collect natural history data over a long period of time.

- It is important to agree on a common set of markers and information to collect, but this may be less challenging than agreements for biorepository samples. Note that a registry can be broader and collect clinical information on patients who don't meet the entry criteria established for repository.
- Are there any initiatives that could be developed in the preclinical space, e.g., on animal models and translation into clinical studies? Is there any benefit to standardizing animal models, or would that be specific to the mechanism of action under study?
  - It likely will not be useful for everyone in the field to use the same animal models because of different therapeutic approaches. However, there could be benefit to understanding which animal models align with which human disease subset (as measured by gene expression profile), as has been done for liver cancer models.
  - There are also ongoing efforts to standardize the standard operating procedure for animal models, including route of administration, dosing, frequency, and strain variability

### **Working Group Proposals, Summary & Next Steps**

Moderators: Gary Burgess, Veronica Miller, and Arun Sanyal

The preceding sessions covered three opportunities for collaboration, a clinical registry, a biorepository, and data standardization. Two working groups can be formed initially to address issues at the foundation of the three collaborative opportunities.

- A Definitions Working Group will develop definitions for disease progression (e.g., NASH, fibrosis), and diagnosis / identification of target patients (e.g., high-risk NASH

patients). These definitions will be critical to data standardization efforts and entry criteria for the biorepository.

- An Informed Consent Working Group will develop standardized informed consent templates, including minimal elements to allow patients to opt in or opt out of sharing of their samples and data.
  
- Other items to note for next steps:
  - Recruit additional participants to the Liver Forum, including pathologists
  - Explore possibility of meeting with FDA through the Critical Path Innovation Meeting
  - Explore establishment of a commonly accessible website or discussion forum for interaction of Liver Forum members