THE FORUM FOR COLLABORATIVE RESEARCH

PSC FORUM 2

Summary of Proceedings

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THE FORUM
For Collaborative Research℠

Berkeley School of Public Health

CONTENTS

SESSION I: OVERVIEW & PSC PROJECT UPDATES

Welcome and Introduction

Presenter: Jessica Weber, *Forum for Collaborative Research*

Introduction to the Forum for Collaborative Research:

- The Forum for Collaborative Research (the Forum) is a public/ private partnership founded in 1997 to advance the field of HIV drug development.
- The Forum's mission is to facilitate the regulatory sciences by providing a neutral and independent venue for ongoing multi-stakeholder dialogue to promote research and treatment.
- The hallmark of the Forum is the inclusion of all stakeholder groups, including patient and advocacy organizations, academia, federal agencies, industry, professional societies and other relevant entities.
- The Forum's HIV collaborative model was successful and, as a result, it has been applied to other conditions, such as HCV, HBV, CMV, NAFLD/ NASH and most recently PSC.

PSC Forum:

- A multi-stakeholder Steering Committee leads the Primary Sclerosing Cholangitis (PSC) Forum; they are charged with identifying key project areas and guiding ongoing discussions, in order to advance the regulatory science. When an in-depth review is needed on specific topics, the PSC Forum can establish working groups.
- Currently, there are three working groups, the PSC Patient Databases Working Group, the PSC Inclusion/ Exclusion Criteria Working Group, and the PSC PRO Tools Working Group.
- PSC Forum 1 had 63 people registered, of which 60 people attended in person and three attended remotely.
- The evaluation from PSC Forum 1 indicated that the vast majority of participants in PSC Forum 1 strongly agree or agree that the meeting was valuable and they would recommend joining to a colleague.
- The PSC Forum is sponsored by the DURECT Corporation, Gilead Sciences, NGM Biopharmaceuticals, and TARGET PharmaSolutions.

PSC Patient Databases Working Group Update

Presenter: Rachel Gomel, *PSC Partners Seeking a Cure*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_I-_Gomel.pdf

- The goal set for the PSC Patient Databases Working Group is to create a list of current PSC databases, define the purpose of each, identify the information being collected,

determine information gaps, and suggest other fields that could be included. Subsequently, the working group learned that harmonization efforts for PSC databases were already under way.
- The working group created a list of registries, which should also include the PSC Registry and Biobank at Helsinki University led by Dr. Martti Färkkilä.
- Since harmonization efforts are already underway, the working group requested that the Forum create a webpage listing PSC registries. The goal of this work is to sensitize and inform PSC patients about registries available to them and to encourage researchers to engage in collaborative data sharing. This webpage is now available on the Forum website and four registries have responded with their information: the CALID Registry, PSC Partners Registry, the European Reference Network, and the UK-PSC Database and Biobank. Information being collected includes an overview, requirements to join the registry, geographic area the registry covers, other pertinent information and a contact.
- One example is the PSC Partners registry, which houses data on 1200 PSC patients. The registry crosses national and institutional boundaries, and it includes PSC patients treated in nonspecialized centers.
- The immediate next step for the PSC Patient Databases Working Group is to obtain information on each of the PSC databases. The larger goal is to inform patients and families, as well as promote growing collaboration and harmonization of patient registries.

PSC PRO Working Group Update

Presenter: Douglas Thorburn, *Royal Free Hospital*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_I-_Thorburn.pdf

PSC PRO Working Group Update:

- The working group met once and included presentations by Martine Walmsley on behalf of PSC Support, Michelle Campbell on behalf of the Food and Drug Administration (FDA), Steve Rossi and Rob Myers on behalf of industry.
- Ms. Walmsley described aspects of living with PSC from the patient perspective and the importance of measuring it over time. While there are quality of life tools for other disease areas, a tool is still needed for PSC.
- Ms. Campbell discussed the FDA's processes for developing patient reported outcomes (PROs), highlighting that early involvement with the FDA was crucial. The FDA is very supportive of a PRO in relation to PSC. She also highlighted the concepts of context of use, establishing a vision for the goal of the tool, the importance of accurately measuring specific aspects of disease that might be modifiable by treatment, and specific treatments according to their mechanism of action.
- Dr. Rossi described PROs specifically related to NGM Biopharmaceutical's work in PSC, particularly related to the symptom of itch.

- Dr. Myers recounted Gilead's experience in developing a PRO for PSC as part of the simtuzumab study. The tool has 42 questions and takes approximately 10 minutes to complete; it will be further validated in the phase 2 Gilead study of the FXR agonist.
- There was general agreement on the need for a validated PRO for PSC. The discussion also brought attention to the dichotomy between clinically significant and statistically significant changes in symptoms, as well as on how these changes relate to the patient experience.
- The suggestion to build quality of life measures around specific aspects of PSC was explored. These measures could be modified to provide information on effectiveness of treatments.

PSC Quality of Life Measure Update:

- During PSC Forum 1 Ms. Walmsley presented an outline of the PSC quality of life tool under development in the United Kingdom (UK), and Dr. Thorburn provided an update. Similar to other PROs, there are three phases of development. Phase one involves generating a list of issues. Phase two involves constructing the questionnaire, and phase three involves validation. Currently, this measure is finishing phase one.
- Over 1,000 items related to quality of life were identified, and this list has been reduced to 390 issues, which are undergoing evaluation in focus groups among a wide range of PSC patients. In April, clinicians will be included in the discussion, and a questionnaire is expected to be constructed by Fall.
- Finally, it is important to note that this work has been made possible by funding from the British Liver Trust, PSC Partners Seeking a Cure, and PSC Support.

SESSION II: SESSION TITLE

PSC Project and Inclusion/ Exclusion Criteria Working Group Update

Presenter: Gideon Hirschfield, *University of Birmingham*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_I-_Hirschfield.pdf

PSC Inclusion/ Exclusion Criteria Working Group Update:

- This working group involved clinicians, patients, industry, and regulators to discuss the inclusion/ exclusion criteria across multiple studies with the goal of establishing a smooth transition and to hasten trial development.
- A challenge with PSC is its heterogeneity and its numerous phenotypes.
- During the working group, Intercept Pharmaceuticals noted that PSC has received an orphan drug designation. A number of patients receive ursodeoxycholic acid (UDCA) as treatment, perhaps more than 50%, which could be considered a confounder for clinical trials. Clinical trials also have difficulty with PSC-related definitions, one being

"dominant strictures". Additionally, the exclusion of cancer diagnoses affect the populations included in trials.
- Comorbidities have been a challenge in PSC clinical trials.
- It has been very informative for the working group to learn more about trial design for industry, the influence of regulators, and rationale. There would be substantial benefits to harmonizing when possible.

International PSC Study Group (iPSCSG) Update:

- The iPSCSG has a long history of research in PSC and is academic-led.
- The iPSCSG will meet at EASL. The host center moved from Oslo to Amsterdam. Ulrich Beuers and Cyriel Ponsioen are now leading the organization, and it has a number of working groups, which in some ways parallel the PSC Forum.
- The iPSCSG is working to establish definitions for PSC, based on a DELPHI process. Although they have met previously, the discussion shifted to a focus on guidelines rather than definitions. The group will meet again to further discuss diagnosis, inflammatory bowel disease (IBD), phenotypes, staging of liver disease, etc, and will continue to refine the process.

Discussion:

- The importance of establishing a Global PSC Registry was highlighted; it was previously very useful in Primary Biliary Cholangitis (PBC) research and encouraged progress for a second line therapy. Once a global registry is created, it can collect data on thousands of patients, gather information on biochemistries, imaging and allow for subgroup analysis.
- Dr. Dimick-Santos agreed that a registry capturing numerous patients, symptoms, lab values, and clinical outcomes would be beneficial. The global PBC study group provided data that led to the acceptance of alkaline phosphatase (ALP) as a surrogate for outcomes. However, there are currently not enough data sets from PSC patients to support this level of data analysis.
- Dr. Hansen described the Global PBC Registry indicating that it's collecting retrospective data and that it continues to grow. Input from the FDA and EMA on a Global PSC Registry would be helpful. Dr. Dimick-Santos suggested that a database could be further discussed during a Critical Path Innovation Meeting (CPIM). Dr. Schabel also indicated that there is a similar process within EMA called the Innovation Task Force (ITF).
- Dr. Miller stated that listing PSC databases would support patient education, but establishing a Global PSC Registry could be the next step in advancing PSC research.
- One participant noted that continuing a placebo arm in long-term studies can be a challenge, especially relating to retention.

SESSION II: REGULATORY PERSPECTIVES

Biomarkers of PSC Disease Progression

Presenter: Lara Dimick-Santos, *U.S. Food and Drug Administration*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_II-_Dimick-Santos.pdf

- Dr. Dimick-Santos stated that the article, "Design and Endpoints for Clinical Trials in Primary Sclerosing Cholangitis," was developed from the American Association for the Study of Liver Diseases (AASLD)/ FDA workshop, and is available online through the journal of *Hepatology*. The paper is data-driven and explains the advantages and disadvantages of potential endpoints that could be used in various PSC outcomes.

FDA: PSC Regulatory Updates

Presenter: Veronica Pei, *U.S. Food and Drug Administration*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_II-_Pei.pdf

- Dr. Pei clarified that there were minimal regulatory updates, but that the session would be used to clarify the discussion of endpoints from PSC Forum 1.
- Dr. Pei reviewed the status of PSC clinical trials listed on clinicaltrials.gov. Two trials will be starting to recruit. Six trials are in the process of recruitment, and four additional trials are not yet recruiting. Dr. Pei presented a tabular summary of this information, and noted that the majority of trials are in Phase 1 or Phase 2.
- She indicated that in the majority of studies ALP is the primary endpoint. Following up on the regulatory update from PSC Forum 1, Dr. Pei reviewed the types of endpoints that the FDA uses to support approval pathways. The first type of endpoint is *clinical benefit*, which is used to support the regular approval pathway. It is defined as an endpoint that describes how a patient feels, functions or survives. The second type of endpoint is a *validated surrogate*, which is used to support the regular approval pathway; it has been validated by randomized control trials (RCTs) and can be relied on to show that the surrogate endpoint is able to predict or correlate with the clinical benefit. The third type of endpoint is the *surrogate endpoint*, which is reasonably likely to predict clinical benefit; it is used to support the accelerated approval pathway.
- Dr. Pei stated that there is currently not enough evidence to support the use ALP as a standalone surrogate endpoint. Yet, ALP could potentially be used as part of a composite in the future. The FDA noted their flexibility to discuss PSC endpoints and indicated that a determination would be made on an individual basis.

EMA: Regulatory Update from Europe

Presenter: Elmer Schabel, *European Medicines Agency*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_II-_Schabel.pdf

- Dr. Schabel indicated that European Medicines Agency (EMA) will publish a reflection paper on chronic liver conditions including PSC, likely at the end of the second quarter in 2018; a stakeholder interaction is currently being planned for December 2018.
- Dr. Schabel highlighted potential PSC surrogate endpoints, and addressed the preliminary regulatory position. ALP is likely to be a reasonable surrogate; however, results from the Urso and simtuzumab studies raise questions about whether ALP alone can be predictive. Transient Elastography (TE) and bilirubin would require further validation. Histology and the combination of ALP and histology are the most likely surrogate endpoints. The regulatory guidance must still determine how to evaluate histology and ALP, but favor co-primary and responder-type evaluation. For histology, staging based on the Nakanuma Score is suggested but other scoring systems are also acceptable; EMA is still determining if this endpoint should be evaluated based on improvement or non-deterioration.
- The guidance document is still considering the study duration for disease treatment, which is proposed for at least two years, but may depend on the investigational compound, patient population, etc. For trials focused on symptom management, a study duration of six months will likely be considered acceptable. The symptomatic effects as well as influence of a treatment on quality of life should be demonstrated.
- The guidance document is in the process of resolving remaining concerns before being finalized.

Discussion (General):

- The importance of specific regulatory guidance was highlighted by participants; any increase in clarity is beneficial for the clinical development process, and ultimately for patients.
- One participant questioned the flexibility of the accelerated approval pathway. Regulators acknowledged that PSC patients have variable needs and PSC has differing disease targets. They are willing to provide feedback but may seek appropriate justifications for decision making.
- There was a proposal to include a presentation relating to the IPSCSG activities in the future.
- A patient organization advocated for PROs and registries to be translated into various languages and across cultures.

Endpoints:

- Dr. Dimick-Santos noted that the choice of endpoints depends on the phase of drug development, mechanism of action or the drug's intended treatment. As an example,

ALP would be more reflective of an anti-inflammatory drug than one that focuses on bile duct injury. Whereas, histology may look at the inflammatory process in the liver parenchyma and fibrosis stage.

- Similar to NASH, an antifibrotic drug may not be the most useful for long-term treatment because it may not attack the underlying disease. However, to maximize the patient benefit, it may be most successful to create a combination treatment involving an anti-fibrotic drug with one that affects the underlying disease or disease process.
- Regulators indicated that registry data can be useful to support a surrogate, but may not provide enough information to validate it. Instead data would be needed from controlled clinical trials.
- Dr. Dimick-Santos encouraged organizations conducting clinical trials in PSC or other liver diseases to send the FDA their phase 2 datasets. They are being analyzed and may provide important information on endpoints, such as ALP.
- A participant suggested that the Forum could promote dialogue among the PSC community to define approvable endpoints. Additionally, focusing on certain subsets of patients and identifying a specific approach to symptoms, such as pruritus, may advance treatment.

Registries:

- Similar to the Liver Forum, initiating a placebo arm for the PSC Forum could yield useful data from ongoing studies. Additionally, planning for an extended placebo arm could promote greater natural history data. Since PSC is a heterogeneous disease, analyzing data on subpopulations could enhance the understanding of surrogate endpoints. The Global PBC Registry collects retrospective and prospective data and provided key insights to the PBC community. Along these lines, TARGET PharmaSolutions is collecting retrospective and prospective data on PSC patients submitted by doctors and clinical centers.
- Dr. Hirchfield indicated that the UK-PSC registry collects retrospective data, but will be working with NHS Digital to collect additional patient information. However, there is also urgency to expand the registry to include prospective data in the future.

SESSION III: CLINICAL TRAIL MANAGEMENT

The Patient Perspective

Presenter: Ricky Safer, *PSC Partners Seeking a Cure*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_III-_Safer.pdf

- PSC Partners Seeking a Cure was founded in 2005 with the dual goals of providing education and support to PSC patients, families and caregivers as well as raising funds to research causes, treatments and a cure for PSC.
- PSC Partners Seeking a Cure gains insight into the patient experience through their patient registry. In advance of PSC Forum 2, they surveyed registry participants to

learn about specific gaps in communication between clinicians and patients, and how to better address PSC patient's concerns about participating in clinical trials. The survey was sent to 1194 patients, with 402 responses.

- Of the respondents, only 20% had participated in a clinical trial, and about 50% of these participants rated their trial experience as a 10/10. Patients attributed their poor clinical experience to being treated like a "guinea pig," lack of follow up, not receiving results, lack of information about how the research itself was progressing, lack of transparency, and being dropped after the trial was over.
- Since 80% of the respondents have not yet participated in clinical trials, it is crucial for researchers to understand their concerns. The most common concerns that patients expressed were general fear of the unknown, unknown side effects or long-term effects, possibility that the drug might affect current treatment for concurrent diseases, being in the placebo group, decreasing their chance for a transplant, disruption to their daily family life, and fear of jeopardizing their current quality of life. A large number of PSC patients stated that they did not have concerns about enrolling in a clinical trial.
- Patient's indicated that they were most likely to seek advice on trial enrollment from their hepatologist, with the second most common source of information being an online search.
- Before agreeing to participate in a clinical trial, patients wanted a clear understanding of the advantages and disadvantages of participation, and an estimate of the time commitment. During the trial, patients would like to be able to contact their physicians about any concerns. After the completion of the trial, patients requested that researchers share trial results directly, and some indicated that reimbursement for travel and missed time from work would further encourage participation.
- Some patients are willing but ineligible for a trial. Expanding inclusion/ exclusion criteria to include more patients, possibly including decompensated patients may increase recruitment.

Academic Perspective on Trials

Presenter: Gideon Hirschfield, *University of Birmingham*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_III-_Hirschfield.pdf

- Dr. Hirschfield noted that it can be difficult to get patients into clinical trials, because of PSC's heterogeneity. A number of obstacles to patient enrollment cannot be modified for regulatory reasons, industry reasons, and to ensure delivery of a safe healthcare environment.
- Similar to Ms. Safer, Dr. Hirschfield agreed that a patient's hepatologist plays a key role in getting patients involved in clinical trials.
- One challenge of the disease is the length of time to reach an endpoint, which can be 10-20 years after diagnosis.

- Patients may not be able to participate in a clinical trial due to other factors in their lives, such as school or family commitments. Additionally, since reimbursements are often limited to travel and hotel stay, it may be costly for participants to take time off work. Along these lines, physicians should advocate for better reimbursement policies for patients.
- Retention has generally not been an issue in PSC clinical trials.
- Screen failure rates vary. Some patients will not be screened for participation, if they will be ineligible for participation. While there remains more to learn about the relationship between ALP values and PSC, ALP is a factor in eligibility and screen failure rates.
- Colonoscopies are often required at greater frequency for trial enrollment than the standard of care indicates.
- When conducting clinical trials, sponsors should consider re-screening patients with screen failures, if possible.

NGM282 Phase 2a Study in PSC

Presenter: Steve Rossi, *NGM Biopharmaceuticals*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_III-_Rossi.pdf

- NGM Biopharmaceuticals is conducting a phase 2a proof-of-concept study to understand the biologic activity and safety. Establishing the protocol involved discussions with numerous experts and patient advocates.
- The overall screen failure rate was about 35%, which is relatively low for PSC studies.
- Enrollment criteria is challenging; it should be as broad as possible, but balanced to incorporate subsets in terms of safety, and reflect the potential for different outcomes.
- NGM282 is a biologic, which reduces the likelihood of hepatic impairment issues, and other drug interactions. Patients were included in the study on medications for other comorbid conditions unrelated to the IBD biologic activity.
- Dr. Rossi explained several criteria for study enrollment including methods of PSC diagnosis, and requirements related to dominant strictures and IBD. He outlined additional laboratory parameters as well. As a note, at enrollment approximately 60% of patients were taking UDCA, and were included in the study if the dosage was stable over time. Patients were stratified by UDCA usage or no UDCA usage at baseline. Certain subpopulations of PSC were also included, such as patients with autoimmune overlap or patients with features of autoimmune hepatitis, and compensated cirrhosis.
- Some patients with cholangitis and flares of IBD were rescreened and included in the study.
- NGM Biopharmaceuticals presented further data on this study at a late breaker abstract session. Overall, Dr. Rossi noted no differences in outcomes or safety signals during the study in any of the subpopulations. He also indicated that the enrollment criteria allowed for broad participation and promoted an inclusive study protocol.

Patient Recruitment and Retention in Phase 2 PSC Studies

Presenter: Rob Myers, *Gilead Sciences, Inc.*

Slides:
http://forumresearch.org/storage/documents/PSC_Forum/psc_forum_2/Session_III-_Myers.pdf

Simtuzumab Study:

- The simtuzumab study involved a number of procedures including liver biopsies at baseline year one and year two as well as MRCPs at the same frequency.
- Major inclusion criteria included chronic cholestasis for at least six months, and liver biopsy as well as an MRCP during screening consistent with PSC. Patients with other causes of liver disease and significant transaminitis or renal dysfunction were excluded. Some patients with cholangitis and flares of IBD were rescreened and included in the study.
- Major exclusion criteria involved patients with a history of decompensated liver disease, other liver diseases and active IBD. However, the IBD criteria changed over the course of the study. Regulators had initially raised concern that simtuzumab could have an impact on wound healing, based on its mechanism of action; as the study proceeded, this did not develop into a significant concern allowing for broader participation.
- Other exclusion criteria included cholangiocarcinoma (CCA), ascending cholangitis within 60 days, indwelling drains or stents, and patients with open wounds or who had a major surgical procedure within 30 days due to the potential issues of wound healing.
- The screen failure rate for the simtuzumab study was about 21%. The most common reason for screen failures was due to liver biopsy not consistent with PSC, followed by active ulcerative colitis.

FXR agonist (GS-9674):

- The GS-9674 study expanded the inclusion criteria from simtuzumab based on lessons learned.
- The purpose of this study was to determine the safety, tolerability and efficacy of GS-9674 in patients with PSC. Patients included in this study were non-cirrhotic, with an ALP at least 1.67 times normal at baseline. They were required to have a cholangiogram demonstrating PSC within 12 months, be on a stable dose of Urso for at least 12 months, and IBD patients had to have a stable dose of immunosuppressants for at least three months.
- The major exclusion criteria were ALP 10 times above normal, evidence of cirrhosis, active IBD, small duct PSC, patients with a history of liver transplantation, Hepatocellular Carcinoma (HCC), or CCA. Patients on antibiotics, specifically for PSC were also excluded.
- The screen failure rate was about 10%, largely due to prescreening. The most common reasons for screen failures were low ALP, and lack of cholangiography evidence of PSC within the prior 12 months.

- This study involved a highly motivated patient population with an 83% retention rate. Reasons for withdrawal included adverse events, withdrawal of consent or protocol-specified.

747-207 AESOP Overview and Inclusion/ Exclusion Criteria

Presenter: Rich Pencek, *Intercept Pharmaceuticals, Inc.*

Slides:
http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Session_III-_Pencek.pdf

- This study was a Phase 2 randomized placebo-controlled trial, evaluating the efficacy and safety of obeticholic acid (OCA) in patients with PSC. Notably here, patients were randomized in a 1:1:1 manner to treatment with either placebo, low-dose OCA at 1.5 mg daily or high-dose OCA at 5 mg once daily. Following the completion of the double-blind phase of the trial, patients had the option to continue on in an open label extension.
- The primary endpoint for the study was change in ALP and there were several secondary endpoints, such as other liver biochemistry, markers of hepatic fibrosis, FXR activity, IBD symptoms. Patients were required to have an ALP twice the upper limit of normal for inclusion in the study.
- Bilirubin was required to be under 2.5 times the upper limit of normal, to exclude dominant strictures, which were significant barrier to enrollment. As a result, the protocol was altered to exclude only dominant strictures that "are considered clinically relevant in the opinion of the investigator".
- The inclusion/ exclusion criteria were mainly based on confirmation of PSC diagnosis and ruling out of other forms of PSC. IBD was included in the study but required to be stable and well controlled. Patients on Urso were included in the study but capped at no more than 50% of the cohort, and patient's taking high doses were excluded. Patients on prophylactic antibiotics were included, and patients taking fenofibrate or other potentially hepatotoxic medications were excluded.

Discussion (General):

- A European PSC patient organization noted that they discussed creating better information for patients related to clinical trials with the Dutch Central Committee for Research. They also suggested that the Ministry of Health include participating in clinical trials as part of the high school curriculum.
- Dr. Boyette from Curable indicated that their organization has been working with the University of Pittsburgh Medical Center to conduct patient and physician education related to early evaluation for PSC transplant.

Recruitment and Retention:

- The group considered various factors affecting clinical trial participation. The survey conducted by PSC Partners Seeking a Cure indicated that 83% of patients considered

their hepatologist's opinion as the most important factor in study participation. Patient communities can play a powerful role in clinical trial participation and education. Ms. Walmsley stated that in the UK patients may change hospitals and/ or doctors in order to join a clinical trial, rather than seek a referral.

- One participant noted differences between the Europe and the United States in patient recruitment and participation. In Europe, there are higher screen failure rates at academic institutions largely due to a more complex patient population. In the United States, recruitment is often from large gastrointestinal private practice groups with more stable patients.
- Dr. Dimick-Santos suggested that the Forum in conjunction with patient groups reach out to physicians, including hepatologists and gastroenterologists, to highlight the importance of clinical trial participation.
- As previously stated, patients should receive the study allocation information, as soon as it is possible to share. Additionally, patients should be reimbursed for their time and their travel to improve and encourage recruitment. One suggestion to further this goal would be to create a charity paid for by the study's sponsors, which could administer these funds to individuals as needed.
- Another suggestion for promoting recruitment and retention of PSC patients was to create a flexible clinical trial, which could allow for patient participation outside of work hours or on weekends. Patients could also receive a credit card to charge any expenses incurred by the clinical trial, such as travel or parking.
- Along these lines, laboratory tests, such as blood samples, could be collected at a patient's home. However, the FDA cautioned that in early phase trials patients may need closer monitoring to establish the safety and stability of a drug.
- Some approaches may be constrained by internal review boards (IRBs), due to concerns about inducement.

<u>Endpoints:</u>

- Dr. Kowdley highlighted differences in the studies indicating that each one had different requirements for ALP, Urso use, and how PSC was diagnosed.
- Dr. Dimick-Santos suggested stratifying enrollment criteria to include patients with normal ALP in clinical trials, which is an approach previously utilized in PBC clinical trials.
- The ideas of combining ALP to form a composite with other endpoints and establishing a Global PSC registry were reiterated.
- One participant questioned whether ALP will continue to be used as an endpoint and noted that endpoints for PSC have been moving towards fibrosis. Ultimately, endpoints will depend on the goal of the drug and the mechanism of action. In the future, drugs could be combined to more effectively treat different aspects of the disease.
- The panel was asked about potential exploratory endpoints, specifically focused on bile ducts, for future research. Dr. Myers indicated that they had reviewed MRCP and reconstruction of the biliary tree with MRI, but found that it was not sensitive for predicting disease progression. They have also collected stool for microbiome and bile acids, but it will be analyzed at a later date.

<u>Fecal Calprotectin:</u>

- The panel was asked about whether fecal calprotectin had been evaluated as a tool for assessing PSC disease activity instead of colonoscopy. However, colonoscopy serves several purposes: it generates a Mayo Score, assesses dysplasia, and addresses the concern that patients will develop colon cancer as an adverse event during a clinical trial.
- Fecal calprotectin has been collected in several recent PSC studies, but has not been considered as part of the inclusion or exclusion criteria.
- The specificity of the fecal calprotectin level depends on the threshold set for detecting active disease. If the level is too low, the test will detect false positives; if the fecal calprotectin level is sufficiently high, the results can delineate active disease. However, it was suggested that this method may be more useful for risk stratification than for linear monitoring.

SESSION IV: WRAP-UP

Additional Topics for Discussion

Moderator: Veronica Miller, *Forum for Collaborative Research*

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/psc_forum_2/Miller-_Session_IV.pdf

The group considered potential topics for future meetings or working groups.

- They revisited the importance of establishing a Global PSC Registry, and highlighted the value of sharing clinical trial data.
- HCC was proposed as a topic for future discussion. However, PSC patient advocates indicated their preference for a focus on the diagnosis and prevention of CCA, since it is a greater unmet need. Yet, this disease is a rare event, making it difficult to study. A Global PSC Registry, containing biobank data, could provide useful information, which can help establish prediction rules and identify patients at higher risks. Regardless, further natural history data is important for HCC and CCA.
- One participant cautioned against using clinical trial data to establish natural history on CCA, since they are biased to exclude patients with risk. Instead, the focus should be on diagnostics for CCA.
- The number of patients diagnosed with CCA is small, with the majority being diagnosed during initial PSC diagnosis and in the first year, making it even more difficult to gather natural history data through a registry. It may be complex to receive approval for a medication used to prevent cancer.
- Dr. Boyette stated that her organization was in the early stages of creating a lab, which uses dogs to screen patient samples for CCA. The goal of this work would be to develop laboratory biomarkers for chemo prevention strategies. The FDA indicated that they were supportive of innovation. The FDA's Critical Path Innovation Meeting or EMA's Innovation Task Force can provide further guidance on regulatory considerations.
- Non-invasive biomarkers, such as measures of liver stiffness, should be further discussed in a working group. Additionally, the Forum could consider developing the

topic of MELD scores as a surrogate endpoint in patients with more advanced disease. Yet, it may be difficult to extrapolate MELD scores. Patients with PSC may have a significantly better prognosis than other chronic liver conditions with the same MELD score.

- One topic previously suggested for discussion was to focus on the various perspectives of investigators, sponsors, and patients. However, the most recent session on patient recruitment, retention, eligibility and screen failure rates has already addressed this subject.
- Innovative statistical approaches should be discussed at a future meeting and could include response rates or reference best practices in other fields, such as rare cancers.
- The Forum could revisit the FDA/ AASLD article, “Design and Endpoints for Clinical Trials in Primary Sclerosing Cholangitis” to promote further discussion of the paper.
- A discussion of combination treatment should be considered in the future and may include a medication that improves symptoms in conjunction with one that affects disease progression. However, regulatory approval may be easier to attain for individual medications rather than for combination treatment.
- One participant noted that the Forum should consider addressing issues related to pediatric drug development for PSC, which must include the prospect of benefit for regulatory approval from the FDA.