PSC Forum 1:
Summary of Proceedings

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Facilitating Collaborative Research in Drug Development and Health Policy
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For more information or questions about the PSC Forum, please contact Jessica Weber at jweber@forumresearch.org, or visit our website at http://www.hivforum.org/projects/psc-forum

SESSION #1: OVERVIEW & PSC PROJECT UPDATES

Moderators: Veronica Miller, Forum for Collaborative Research
Keith Lindor, Arizona State University
Rob Myers, Gilead Sciences, Inc.

Welcome & Introductions

- Veronica Miller welcomed everyone to the first PSC Forum in-person meeting.
- Keith Lindor and Rob Myers, Co-chairs of the Steering Committee, noted that there has been progress in guidance on appropriate endpoints but there remains a persistent unmet need in PSC.

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/session%20i-%20miller.pdf
Presenter: Veronica Miller, Forum for Collaborative Research

Introduction to 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 Forum collaborative model involves experts from across the community including academics, industry representatives, regulators and patient advocates. These stakeholders are tasked with identifying knowledge gaps and mechanisms to address these gaps. Over time, trust builds allowing for the discussion of more challenging issues.
- The Forum's HIV collaborative model was successful and, as a result, it has been applied to other conditions, such as HCV, HBV, CMV, NASH and most recently PSC.

PSC Forum:

- This Forum was initiated based on the March 3-4, 2016 *Trial Design and Endpoints for Clinical Trials in Adults and Children with PSC* meeting sponsored by the U.S. Food and Drug Administration (FDA) and the American Association for the Study of Liver Diseases (AASLD). The Forum received requests to provide a venue for the continuation of this work.
- A multi-stakeholder Steering Committee leads the PSC Forum by 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 two working groups, the PSC Patient Databases Working Group and the PSC Inclusion/ Exclusion Criteria Working Group.
- PSC Forum 1 had 63 people registered, of which 60 people attended in person and three attended remotely.
- The PSC Forum is sponsored by the DURECT Corporation.

PSC Project Updates

Slides:http://www.hivforum.org/storage/documents/PSC_Forum/01_psc%20ie%20criteria%20presentation.pdf
Presenter: Gideon Hirschfield, University of Birmingham

PSC Inclusion/ Exclusion Criteria Working Group Update:

- The goal of this working group is to examine inclusion and exclusion criteria for PSC clinical trials, consider the evidence in support of the criteria and recommend standardized criteria when appropriate.
- The working group reviewed the inclusion/ exclusion criteria for the AESOP study on obeticholic acid by Intercept.
- An opportunity to review additional protocols across the industry may include Gilead Sciences, Inc. and NGM Biopharmaceuticals.
- Future topics for the working group to discuss include underlying inflammatory bowel disease, concomitant therapies, frequent episodes of ascending cholangitis, use of ursodeoxycholic acid (UDCA) and therapeutic targets for PSC.

International PSC Study Group (iPSCsg) Definitions Update:

- The iPSCsg is engaged in an ongoing Delphi process to create a manuscript with PSC definitions. The outline of the article includes a methodology section, the process of PSC diagnosis, IBD, phenotypes, stages, endpoints, symptoms, and post-transplant.
- The target for the definitions manuscript is to be presented to the larger iPSCsg during EASL 2018.
- The PSC Forum will also be updated on the definitions manuscript moving forward.

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/session%20i-%20safer.pdf
Presenter: Ricky Safer, PSC Partners Seeking a Cure

PSC- Specific ICD-10 Code:

- Although Primary Biliary Cirrhosis (PBC)[1] currently has an ICD-10 code, PSC is categorized under the code K83.0, which refers to cholangitis.
- The rationale for establishing an ICD-10 code for PSC includes the facilitation of studies, establishing a cohort of patients, identifying and assessing therapeutic outcomes, improving information on comorbidities and adverse effects and understanding the burden on patients.
- PSC Partners Seeking a Cure submitted a proposal for a PSC specific ICD-10 code to the ICD Coordination and Maintenance Committee at the Centers for Disease Control and Prevention (CDC). They testified regarding the importance of obtaining an ICD-10 code for PSC on September 13, 2017 and a comment period is open until November 13, 2017. Letters of support from medical professionals are encouraged.
- To simplify the comment process, the Committee indicated commenters should not reference PBC, to minimize confusion, and that they should not request specific sub-codes for PSC.

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/session%20i-%20walmsley.pdf
Presenter: Martine Walmsley, PSC Support

Quality of Life Measure for PSC:

- The aim is to create a questionnaire to measure the quality of life for people living with PSC. To accomplish this task, PSC Support has followed guidelines from the Quality of Life group at the European Organisation for Research and Treatment of Cancer (EORTC).
- The process is based on three stages. The first stage involves a systematic literature review of existing quality of life tools, which identifies conditions associated with or with similar clinical

[1] Primary Biliary Cholangitis was previously referred to as Primary Biliary Cirrhosis. The ICD-10 code is currently still listed under the condition's original name.

features as PSC. Due to the large number of issues initially identified, rules were developed to refine the list. PSC Support is in the process of reviewing the 341 issues identified in the literature with focus groups and conducting interviews. Stage two involves the issues being developed into questionnaire items, involving a pre-test and structured interviews. Stage three involves a large scale validation.
- PSC Support is working with FDA and EMA as they move forward.

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/session%20i-%20gomel.pdf
Presenter: Rachel Gomel, PSC Partners Seeking a Cure

PSC Patient Databases Update:
- The aim of the working group is to locate and define each PSC patient database, highlight the strengths of each, determine any gaps in information and identify other fields to include.
- The PSC Forum reviewed the current PSC patient databases, including registries and cohort studies, noting lead investigators, locations they operate, numbers of patients and their individual strengths.
- The working group's next step will involve creating a webpage with basic details about each database, to help patient's make an educated decision about their participation.

Discussion

Quality of Life Measure for PSC:
- The quality of life measure will reflect the breadth and complexities of PSC, and serve as a tool in program development.
- A PSC Forum member noted that establishing a tool to measure quality of life in PSC is important but symptoms of liver disease should not be generalized to PSC. The measure needs to take into account specific symptoms, such as pruritus, cancer risk, concomitant conditions and types of radiologic testing that uniquely affect PSC patients.
- One patient advocate noted that the quality of life measure should consider chronic pain, which may result from procedures or surgeries. In the future creating a protocol for PSC pain management, including early interventions with pain management specialists, could help guide clinician's treatment.
- For PSC pediatric patient it may be helpful to include items that can be assessed by a parent or caregiver.
- The quality of life measure may want to consider the frailty index, which is an objective measure that correlates with a patient's morbidity.
- PSC Support was urged to recognize that the quality of life measure may be used by PSC patients in different stages of the disease, which could lead to variable manifestations of symptoms.
- A quality of life tool could be used in conjunction with biomarkers that have not yet been validated as endpoints to establish evidence of the biochemical pathway and measure how patient's respond to a drug.

Patient Perspective:
- PSC patients are very willing to take part in research. A survey by PSC Support previously indicated that about 60% of patients were willing to undergo an invasive procedure, such as a biopsy, to help further research for the disease. However, invasive procedures are uncomfortable and introduce risk to the patient; when possible, non-invasive testing and procedures should be validated.

- PSC Partners Seeking a Cure stated that they would be happy to work with anyone in the PSC community, if they need a patient perspective.
- It is important to include the patient perspective on clinical trial enrollment criteria.
- Industry and regulators were urged to consider that barriers to patient enrollment in studies are unnecessarily time consuming requirements, such as study visits and inconvenient locations for blood draws. Study designs should be innovative to minimize unnecessary demands on a patient's time and increase operational efficiency.

iPSCsg Definitions Manuscript:

- The iPSCsg was encouraged to consider that pediatric patients may have a different PSC presentation or phenotypes than adult patients. Children have a higher percentage of Autoimmune Hepatitis- PSC Overlap Syndrome (AIH-PSC) and fewer dominant biliary strictures. Mark Deneau, a Pediatric Gastroenterologist, is contributing to the iPSCsg definitions article.

Patient Registries:

- Duplications may occur between registries if a patient participants in more than one.

PSC Inclusion/ Exclusion Criteria Working Group:

- The Inclusion/ Exclusion Criteria Working Group should include patient representatives to balance the academic/ clinician perspective.
- It may be also be helpful to include a pediatrician in this working group.
- The inclusion/ exclusion criteria in clinical trials should not remain static but be reevaluated over time in the context of trial outcomes.
- When possible older pediatric PSC patients should be included in studies, since medications are often tested initially in adults and only later involve pediatric populations.
- Registries are an important aspect of drug development but they should also be standardized when possible.
- The FDA commented that there is strong interesting in supporting the rare disease community.
- In the future the PSC Forum should discuss screen failure rates.

SESSION #2: REGULATORY PERSPECTIVES

Moderators: Veronica Miller, Forum for Collaborative Research

FDA: PSC Pathways and Endpoints

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/seo%20final%20slides.pdf
Presenter: Suna Seo, U.S. Food and Drug Administration

Approval Pathways for PSC:

- Regular (or full) approval of a drug is performed with well designed, controlled clinical trials that measure the clinical benefit of a drug.
- Accelerated approval can be granted to a product intended to treat a serious and life-threatening illness if it provides a meaningful therapeutic benefit compared with existing treatments or if no treatment exists. Approval based on surrogate endpoints must be based on adequate, well controlled studies. These surrogate endpoints must demonstrate they are "reasonably likely" to predict clinical benefit. Intermediate clinical endpoints that are "reasonably likely" to predict an effect on morbidity or mortality may also be used in an accelerated approval pathway. Since "reasonably likely to predict clinical benefit," implies uncertainty, generally approval is contingent on a sponsor's agreement to conduct additional post approval (phase 4) studies to verify and define the drug's clinical benefit.

Types of Endpoints:

- There are different types of endpoints:

  - an endpoint that directly measures clinical benefit (i.e., how people feel, function and survive),
  - candidate surrogates (which are under evaluation to use in clinical trials),
  - surrogates reasonably likely to predict clinical benefit (is defined as a biomarker, laboratory measurement, or a physical sign used as a substitute for a clinically meaningful endpoint. The level of evidence necessary to determine whether a surrogate is reasonably likely to predict outcomes is made on a case-by-case basis by the FDA.)
  - validated surrogates (which have been proven to predict clinical outcomes bases on controlled clinical trials, also determined by the FDA based on available evidence. For example, a decrease in hypertension for approval of anti-hypertensive drugs, hemoglobin A1c as a surrogate for trials in diabetes)
- Clinical benefit and validated surrogate endpoints are used for traditional approval. Whereas, "reasonably likely to predict clinical benefit" surrogate are used for accelerated approval. Marketing approval for a product requires that a product be safe and effective with evidence of clinical benefit and also takes into account the total risk and potential benefit of a drug. A surrogate endpoint must be measurable, sensitive and on a pathway to a clinically meaningful endpoint. Evidence in support of a "reasonably likely to predict "surrogate endpoint is based on a matter of judgement and empirical evidence; evidence of pharmacologic activity alone is not sufficient.

<u>Potential PSC Biomarkers and Concerns</u>:

- The mechanism of the drug and the clinical benefit that is targeted must be taken into consideration when assessing surrogate endpoints for acceptability. PSC is mainly a biliary ductal disease but results in liver fibrosis and cirrhosis. Drugs may target either the ductal disease or the resultant liver fibrosis or both. Additionally, drugs may be targeted to symptoms such as pruritus or fatigue. Ideally, a drug would improve the ductal inflammation, ductal fibrosis and the resultant liver fibrosis to improve clinical symptoms and survival.
- A challenge in designing clinical trials for PSC is the lack of biomarkers that have adequate evidence at this time to support that they are reasonably likely to predict clinical benefit. As new evidence becomes available, the FDA will take this into consideration in identifying acceptable surrogate endpoints.
- Alkaline phosphatase (ALP) has evidence that it has predicted clinical outcomes in some trials in patients with PSC; however, ALP was not shown to predict improved outcomes in a high dose UDCA trial; therefore, at this time it may not be acceptable as a stand-alone surrogate. ALP may be acceptable in some situations when supported by other endpoints.
- Histology is also problematic because of the patchy nature of fibrosis pattern in the liver; however, it may be acceptable as a reasonably likely to predict surrogate with supportive evidence from other biomarkers and/ or clinical endpoints.
- Elastography has been approved by the FDA to measure stiffness accurately, but the testing was performed on phantoms with known attenuations and not in cirrhotic liver, and it is not specifically approved to diagnosis or stage liver fibrosis. Currently literature shows that it is not accurate in discriminating stages of fibrosis; however, as newer modalities are being assessed this may change in the near future. Elastography may be useful in assessing progression to cirrhosis and thus may be used as a "reasonably likely to predict" surrogate endpoint supported by other biomarker endpoints.
- Under accelerated approval, a phase 4 trial to verify the clinical benefit of the treatment generally must be underway at the time of marketing approval. Decompensation events, all-cause mortality and liver transplant can be used to measure clinical benefit, but must be clearly defined and adjudicated by an independent blinded committee of experts.

Accelerated Approval Considerations:

The entire design of the accelerated approval program should be discussed with the FDA prior to initiation of the phase 3 studies. This should include a synopsis of the phase 4 post-marketing study plan, to verify and define the clinical benefit, and the statistical analysis plan. For seamless trial designs, in order to adequately control for the type I error rate, studies will need to adjust or split the overall alpha between the two trials. If a single phase 3/4 trial is planned you must use a very small alpha (less than 0.05). Challenges for accelerated approval trials include the need for advanced planning before trial initiation, and the retention of patients in a placebo controlled trial after marketing approval.

- Adaptive trial designs could be leveraged in clinical development programs for PSC.

Other:

- The Prescription Drug User Fee Act (PDUFA VI) was renewed in October and will establish a new Type C meeting dedicated to discussing surrogate endpoints.

Slides: http://www.hivforum.org/storage/documents/PSC_Forum/session%20ii-%20schabel.pdf
Presenter: Elmer Schabel, European Medicines Agency

Regulatory Update from Europe:

- The European Medicines Agency (EMA) has a similar regulatory framework to the United States (US).
- The term accelerated is only used for the period of evaluation of a complete marketing authorization application, and it shortens the time period that the full assessment is taking place.
- Conditional approval in the European Union (EU) is comparable to accelerated approval in the US. Conditional approval is responsive to debilitating, life threatening diseases and rare disorders. At the time of licensing, there must be a conclusion that the risk-benefit balance is positive. Additionally, comprehensive data are not yet available but likely will be in the future.

PRIME:

- This procedure is designed to provide promising medicines the ability to establish an early dialogue between developers and regulators. For smaller companies, they can discuss their pre-clinical data with EMA, while larger companies can present promising clinical data.
- The criteria are similar to accelerated assessment and conditional approval.
- To date, advice has been given on two trials in 2014 and 2016 regarding acceptable composites and follow-up.

Primary Endpoints:

- Necessary properties of a primary endpoint include:
  - that it measures important aspects of concepts most significant and relevant to a patient's condition
  - should be clinically meaningful
  - should be reliable and well defined
  - should be sensitive to the effects of an intervention
  - should be "readily" measurable and interpretable
  - validated surrogate
- Although ALP cannot be used as a stand-alone surrogate endpoint, it can be used in combination with other surrogate endpoints.

PSC Clinical Trials:

- Primary trial design should include a study duration for pivotal trials of 5 years, an increased number of patients, or an increased number of patients in the later stages of PSC.
- Primary evaluation should consist of:
  - histology

- liver transplant, death and clinical cirrhosis related events should be included
- role of malignancies, if clarified

Additionally, the design of the American UDCA study could be acceptable.

Discussion

- The presenters were asked whether the FDA and EMA could be flexible regarding P values and adaptive trial design. The FDA signaled that there would be flexibility with P values, determined on a case-by-case basis, and that they are moving towards openness on Bayesian approaches. The FDA stated that their prior experiences with similar diseases will provide guidance on the path forward for PSC. The statistical planning may vary due to certain factors, such as the drug's mechanism of action or the context of the patient population. However, since no treatment is available regulators recognized the importance of a flexible approach.
- A PSC Forum member noted challenges relating to gathering certain types of historical control data. The FDA indicated that historical control data would involve the collection of clinical, biochemical and imaging elements, and if possible, histopathology data. In the US, currently most hepatologist's do not evaluate PSC patients with liver biopsy, histopathology information may not be available for many patients, and the FDA understands the constraint this places on trial enrollment and endpoints. It is preferred to collect as much data as possible, to characterize disease progression.
- Depending on the elements collected in prospective registration databases, this information could provide valuable insight. However, regulators also indicated that both the FDA and EMA have been reluctant to accept historical control data instead of a similarly defined active treatment group. Accepting historical control data would depend on the criteria and answers to questions such as:
  - Does the population match with the inclusion and exclusion criteria of the trial?
  - Is the patient population comparable?
  - If the population is comparable, can you match the patients adequately?
  - How old are these data?
  - Has the standard of care changed since data collection?
  - Is the disease spectrum similar over time?
  - Does this change the manifestations of the disease?
- Regulators were questioned regarding acceptable durations for phase 3 clinical trials and feasibility. FDA responded, the length of a trial will depend on the context of the trial, and will depend on number of factors. For example, population enrolled, mechanism of action of the drug, and indication sought. At this time, for regular approval of drugs for treatment of PSC a composite clinical benefit endpoint may be acceptable, such as, all-cause mortality liver transplant, decompensation events, and progression of MELD score from < 12 to ≥ 15. Use of a "progression to cirrhosis" on histopathology would require liver histopathology at baseline. For approved via an accelerated pathway, using surrogate endpoints, will require confirmation with a verification trial to demonstrate clinical benefit. The choice of a surrogate endpoint(s) reasonably likely to predict clinical will also vary based indication and mechanism of action and the population being studied. Therefore, each drug/ population/ indication combination requires discussion with the regulatory agencies to discuss the best approach for each particular clinical trial. Regulators recognized the burden for both patients and industry when conducting long term verification PSC trials; however, proof of clinical benefit is necessary to protect from full approval of drugs that are not clinical effective. For regular or full approval the total risks and benefits of the drug in the indicated population must be evaluated.

SESSION #3: CLINICAL TRIAL MANAGEMENT

Moderators: Kris Kowdley, Swedish Medical Center

- Kris Kowdley welcomed the audience. He noted the unmet need and unique challenges of PSC in terms of clinical trial design and complicating factors.

Lessons Learned: Simtuzumab Program

Presenter: Rob Myers, Gilead Sciences, Inc.

Overview of Simtuzumab:

- Simtuzumab is a monoclonal antibody against lysyl-oxidase-like 2 or LOXL2. In pre-clinical models of fibrosis, including biliary fibrosis, there was evidence that simtuzumab had an antifibrotic effect. This effect is a result of LOXL2's involvement with fibrogenesis.
- The aim of the study was to evaluate the safety and efficacy of simtuzumab in patients with PSC.

Study Design:

- The design involved a three-arm study with 234 patients. Patients were randomized at 1:1:1 to receive either a low or a high dose of simtuzumab subcutaneously weekly or placebo. Patients had well-compensated PSC, which was confirmed by biopsy and magnetic resonance cholangiopancreatography (MRCP). They also had inactive inflammatory bowel disease, which was a regulatory requirement. They had a partial Mayo score of ≤2, and they could not be on corticosteroids or anti-TNF therapy. Patients had liver biopsies and MRCPs at baseline year one and year two and were read centrally.
- The demographics and baseline characteristics of study participants as well as the study disposition was presented to the PSC Forum.
- The primary endpoint for the study was the change in hepatic collagen content between baseline and week 96 across groups. The study also reviewed standard liver biochemistry, noninvasive markers of fibrosis, Ishak fibrosis stage, progression to cirrhosis, and PSC-related clinical events.

Data and Results:

- The primary data, which was change in hepatic collagen content, was assessed via morphometry. The results indicated there was no treatment effect or improvement in simtuzumab patients versus placebo on hepatic collagen content. Additionally, the study measured alpha smooth muscle actin expression by morphometry, and there was also no difference in that compound. Further, a subgroup analysis that looked at predictors of changes in collagen content indicated that simtuzumab also was not effective in these groups.
- There were no differences in fibrosis change across treatment groups, with approximately one-third of patients worsening, one-third remaining stable, and one-third improving. About 15% of subjects progressed to cirrhosis throughout the clinical trial. There were also 47 patients who had a PSC-related event, most commonly ascending cholangitis.
- The study conducted a genome-wide association, which indicated that one single nucleotide polymorphism was associated with the change in hepatic collagen content over 96 weeks.
- Patients with a higher baseline alkaline phosphatase had a greater risk of PSC complications. Similarly, there was a significant association between the baseline Enhanced Liver Fibrosis (ELF) score and complications.
- Data on liver stiffness, determined by FibroScan, indicated a 100% negative predictive value for cirrhosis. Other serum markers used for fibrosis staging were less accurate.
- The study indicated that the change in the Enhanced Liver Fibrosis (ELF) over time, 12 weeks from baseline, was a significant predictor of PSC complications. As a result, this could be used as a potential endpoint in future clinical trials.

- The study adapted a score originally reported by Ruiz et al. 2014 to develop a MRCP risk score with ranges from 0- 3 based on beta coefficients from the Cox model. They reviewed the incidence of PSC-related clinical events, and noted a substantial increase in complications as the score increased.
- Ultimately, the data showed that simtuzumab was safe and well-tolerated but not associated with improved fibrosis or clinical events in patients with compensated PSC. However, the study provided valuable information about the natural history and management of PSC, which could help to move the field forward.

Discussion

- The PSC Forum considered the relationship between alkaline phosphatase and PSC patients' prognosis. One unique aspect of the simtuzumab study was that it did not require a patient's alkaline phosphatase levels to be elevated as an inclusion criterion to enroll in the study. However, study results indicated that baseline alkaline phosphatase appeared to be a very strong predictor of outcomes. Dr. Myers noted that requirements related to the use of alkaline phosphatase in studies may vary based on the mechanism of action of the drug being tested. In the simtuzumab study the hypothesis being tested was that the medication would have an antifibrotic effect, which was tested through serial liver biopsies. Yet, in a phase 2 study of an FXR agonist, alkaline phosphatase is an inclusion criterion since it is also a marker of the biologic activity of the compound. One challenge related to alkaline phosphatase is limited information regarding the establishment of thresholds that would indicate concern. Normalization of alkaline phosphatase should be an aspiration, but may be used as a risk stratifier. It will continue to play a role in PSC trials, but likely in conjunction with other variables. In the future, the data from the simtuzumab study could be reviewed to determine the prognosis of patients that had an elevated alkaline phosphatase at baseline that normalized through the course of the study.
- Dr. Myers was asked if FIB-4, a marker of fibrosis, was considered in combination with alkaline phosphatase. Although Gilead Sciences, Inc. has not reviewed the relationship between these markers, they plan to examine the dataset with machine-learning software to determine if there are more complex statistical interactions between the variables.
- Gilead Sciences, Inc. did not discuss using an ELF score as a surrogate marker for the simtuzumab study with the FDA. Additionally, the results of the simtuzumab study did not show that change in collagen content could help predict outcomes.
- Captain Anissa Davis-Williams encouraged anyone with additional questions to contact Commander Cheronda Cherry-France, Acting Chief Project Manager at the FDA, for PSC. She also noted a new PDUFA VI requirement for a meeting background package to be submitted for PSC surrogate endpoints.

SESSION #5: WRAP-UP

Moderator: Veronica Miller, Forum for Collaborative Research

- Dr. Miller noted that there were a number of unanswered questions from PSC Forum 1, and they will be further explored at the next PSC Forum meeting. Materials from the meeting will be available on the PSC Forum website. Finally, the PSC Forum Steering Committee will have a debrief call to discuss next steps.

Meeting Close