



THE FORUM FOR COLLABORATIVE RESEARCH

# PSC FORUM 3

**Summary of Proceedings**

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# SESSION I: PSC FORUM UPDATE

## PSC FORUM PROJECT UPDATES

**Presenter:** Jessica Weber, *Forum for Collaborative Research*

**Slides:** [https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P0\\_2019-PSC-Forum-3\\_Weber.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P0_2019-PSC-Forum-3_Weber.pdf)

- Introduction to the Forum for Collaborative Research (The Forum):
  - Part of the University of California at Berkeley School of Public Health
  - Established in 1997 as a public-private partnership to advance regulatory science through stakeholder engagement
  - Hallmark of The Forum is inclusion of all stakeholder groups, including patient and advocacy organizations, academia, federal agencies, industry, professional societies, and other relevant entities
- Forum perspective: “Once new drug candidates and therapeutic strategies are identified, their safe and efficient development is in the best interests of all stakeholders (most of all, patients).”
- PSC Forum mission: “To facilitate evolving consensus, based on real time scientific development in the areas of appropriate methodologies for novel therapeutic approaches, clinical trial design, and harmonization across the PSC community.”
- Forum Goals:
  - To identify and address gaps and barriers in regulatory science to advance the development of safe and effective treatment of PSC
  - To provide an independent and neutral environment for ongoing multi-stakeholder dialogue
  - To provide scientific guidance to facilitate discussions between industry, regulatory bodies, and the academic and patient communities in the area of PSC drug development
- Meeting Participation:
  - The Forum encourages active participation.
  - Participants are expected to behave professionally.
  - Comments and questions are not for attribution. Everyone attending the meeting is participating as an individual expert, and the opinions expressed do not reflect views of their agencies or organizations.
- Updates since PSC Forum 2:
  - There are several changes to the PSC Forum Steering Committee. Keith Lindor has rotated off as the academic Co-Chair. Kris Kowdley from Swedish Medical Center will now serve as the academic Co-Chair. Rachel Gomel from PSC Partners Seeking a Cure Canada and Stanislav Stoyanov from Intercept Pharmaceuticals have also joined the Steering Committee.
  - The Forum is now operating as a membership organization in relation to industry stakeholders, which requires them to pay a fee to participate.
  - The PSC Forum is now operating under the umbrella of the Liver Forum but maintains its own Steering Committee. Membership in the Liver Forum allows for participation in both Forums.

- PSC Forum Working Groups:
  - PSC Endpoints working group is creating a manuscript
  - The Forum will be launching a Pediatric Cholestatic working group, focused on all cholestatic conditions, not just PSC.
- UK PSC QOL Measure Project:
  - Provisional questionnaire developed by Elena Marcus, a PhD student at University College London, under the supervision of Paddy Stone, Bella Vivat, and Doug Thorburn
  - Approach grounded in European Organization for the Treatment of Cancer (EORTC) guidelines, with modifications specific to PSC
  - Fully funded by patient advocacy organizations
  - Four stages of development for QoL measure:
    1. Identification of the quality of life issues
      - 400 items identified from provisional survey data and systematic literature reviews
    2. Provisional questionnaire construction
      - Further explored via clinician interviews and PSC patient discussions
      - 83 item questionnaire was developed
    3. Pilot testing (acceptability, clarity, relevance, and redundancy of items)
      - international questionnaire development, testing in several centers (1 US and 2 European)
    4. Large-scale validation of questionnaire
  - Status of this work:
    - Stage 3- analysis of the pilot testing data from UK participants
    - international development will take about 18 months
    - final questionnaire expected to be comprised of 40 items

## IQ DILI Position Paper

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**Presenter:** Melissa Palmer, *Takeda*

**Slides:**

[https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P4\\_2019-PSC-Forum-3\\_Palmer.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P4_2019-PSC-Forum-3_Palmer.pdf)

- International Consortium for Innovation and Quality in Pharmaceutical Development (IQ):
  - Non-profit organization addressing scientific and technical aspects of drug development
  - Currently composed of 38 pharmaceutical and biotechnology companies
  - Gathers experts from academia, industry, regulatory science to participate in papers about trial design and drug development
  - Recommendations do not imply any regulatory guidance or mandate
- IQ Drug-Induced Liver Injury (DILI):
  - Subset of the IQ, established in June 2016
  - Currently includes 17 member organizations
  - Works to reach consensus and propose best practices on topics related to DILI
- Article describes the detection, assessment and management of acute DILI in clinical trials for adults with cholestatic liver disease.

Palmer et al. (2019). Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease. *AP&T*, 1-20.

- Challenges inherent in current PSC drug trials:
  - Natural course of PSC includes liver test fluctuations due to biliary sludge in strictured bile ducts and episodes of cholangitis, which may mimic DILI
  - Most PSC clinical trials use elevated alkaline phosphatase (ALP) as an inclusion criterion, as a result the DILI criteria are not applicable and cannot be extrapolated to this population
  - Hy's Law for clinical trials as a screening threshold for DILI
    - an aminotransferase (ALT) greater than 3x normal and total bilirubin (TB) of greater than 2x normal
    - caused by drug and not disease
    - developed for patients with normal livers
- Article recommendations for PSC trials:
  - Utilize 10x the upper limit of normal (ULN) for exclusion criteria
  - Repeat ALP and ALT at least twice before starting to show stability of enzymes and postpone the trial if liver enzymes are too variable
  - Average 2 consecutive screenings and baseline measurement to determine baseline ALP and ALT
  - Absolute values should be reported and analyzed
  - Gamma-glutamyl transferase (GGT) and/ or ALP fractionation should be conducted prior to study start
  - Patients with baseline elevations in total bilirubin (TBL) should be excluded unless Gilbert's syndrome or hemolysis
  - ALT > 5x ULN
  - Measure autoimmune markers
  - Consider symptoms (fatigue, right upper quadrant pain, new or worsening pruritis)
- Article recommendations for monitoring and stopping rules:
  - Examine baseline levels and differentiate between total and indirect bilirubin
  - Examine a stable nadir of enzyme levels (occurs around 3-4 months)
  - Examine liver-related and immunological symptoms
  - Establish and utilize a DILI expert panel to evaluate DILI signals
  - An episode of DILI resulting in hepatic decompensation should lead to drug discontinuation
  - Blood tests should be repeated in 2-5 days if hepatocellular DILI is suspected and 7-10 days if cholestatic DILI is suspected. Exact intervals should be based on the patient condition
- Additional considerations:
  - Give vitamin K to offset fat-soluble vitamin K deficiencies
  - Evaluate for possible hepatitis B reactivation
  - Conduct pill counts and measure pharmacokinetic (PK) values to ensure compliance of underlying drugs (such as URSO) during the clinical trial
  - Decompensated cirrhotics may have different endpoints when it comes to DILI
- Article includes 3 tables:
  - Algorithm for Monitoring and Interrupting study drug for Hepatocellular DILI signals with Normal Baseline ALT Patients who enter the trial with elevated alanine aminotransferase

- Monitoring and interrupting study drug for Hepatocellular DILI signals Elevated Baseline ALT
- Monitoring and interrupting study drug for Cholestatic DILI signals

## IPSCSG & Meta-Analysis for Surrogate Endpoints

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**Presenter:** Gideon Hirschfield, University of Toronto

**Slides:** No slides

- International PSC Study Group (IPSCSG)
  - Published a paper describing a database of over 7,000 PSC patients:  
  
Weismüller et al. (2017). Patient age, sex, and (IBD) phenotype associate with course of PSC. *Gastroenterology* 152, 1975-84.
- International PSC Study Group (IPSCSG)
  - A group of academic clinicians and clinician-scientists working in PSC
  - Meet at least twice per year – once at AASLD (The Liver Meeting) conference and once at EASL (The International Liver Congress)
  - Current Chairs: Cyriel Ponsioen and Ulrich Beuers (Amsterdam, Netherlands)
  - Includes working groups dedicated to biomarkers, transplantation, and outcomes
- Meta-Analysis
  - A small group of lead investigators (including from the UK, Mayo Group, Amsterdam, Toronto, Rotterdam, Belgium, and Japan) are working to pool their data to validate surrogate endpoints and to create optimal risk scores
  - A protocol has been written and will be submitted for ethics approval. It is being shared with people interested in contributing to the meta-analysis. Data sharing agreements will need to be established and each party has expressed slightly different views.
  - A PhD student at the University of Toronto is working on the PSC meta-analysis.
  - The inclusion of stakeholders involved in The Forum (patients, industry, regulatory science) will enrich the meta-analysis and can help develop risk scores
  - Data from clinical trials run by industry will provide additional information related to natural history

## PSC Endpoints Working Group

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**Presenter:** David Assis, Yale University School of Medicine

**Slides:** Not available

- PSC Endpoints Working Group Overall
  - Developed after the Steering Committee noted a limitation of PSC clinical trials in establishing acceptable endpoints
  - Working Group explored several endpoints but focused on PSC patient reported outcomes (PROs)
  - Currently gaps in establishing and validating adequate PROs to capture the wider patient experience and development of PROs that are not symptom specific

- Current PSC PRO efforts:
  - The UK-PSC QoL Measure is being developed as a tool to measure PSC patient's quality of life.
  - A PSC PRO was published in 2018 to measure PSC symptoms and their impact on functioning:

Younossi et al. (2018). Development and validation of a primary sclerosing cholangitis-specific patient-reported outcomes instrument: The PSC PRO. *Hepatology*, 68, 155-165.

  - PSC PROs need to undergo wider validation in a diverse group of patients
  - An analysis needs to take place in the context of real symptoms from IBD, which is prevalent in this population
- Goals of the Working Group's article:
  - Describe gaps in the field of PSC PROs as well as pros and cons of available tools
  - Establish how they have been used in clinical trials to date
  - Discuss perspectives from clinicians, patients and advocates, academia, regulators, and industry
  - Develop a consensus on the proper role of PROs in studies and clinical trials for PSC, with the focus on supporting a pathway towards approval
  - Establish a blueprint for incorporating PROs into PSC trials, particularly the composite endpoints
- Patient Perspectives:
  - Surrogate biomarkers don't always reflect patient experience
  - Currently available PROs are suboptimal
  - A PRO expert should be included in Steering Committee
  - Patient-friendly technology can be used to collect PROs
- Current status of this work: soliciting feedback from stakeholders

## Update from PSC Partners Seeking a Cure

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

**Slides:**

[https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P5\\_2019-PSC-Forum-3\\_Safer.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P5_2019-PSC-Forum-3_Safer.pdf)

- Establishment of a new ICD-10 code for PSC: K83.01
  - Launched in October 2018
  - Will help in understanding the epidemiology and natural history of PSC
  - Conducting educational campaign to encourage use of the code for all new and returning PSC patients
  - Komodo Health, a data software company, studied health insurance claims nationally to track usage of the code; utilization increased linearly from October 2018 (2.7k) to September 2019 (13.4k); geographic distribution represents high population areas with PSC academic centers; currently working to reach small community clinical practices

- Research Grants Program
  - Initiated in 2009 in collaboration with PSC Partners Seeking a Cure Canada
  - Evaluated by Scientific Medical Advisory Committee and awarded annually
  - Allotted over \$3M to date; intended as seed funding
  - Goal is to promote research that addresses a novel or clinical research question related to PSC and other closely associated diseases
  - 2019 recipients are in Spain, Netherlands, Israel, and Mayo Clinic
  - Deadline for next year is January 31, 2020
  - Also offers a Young Investigator Award as a separate mechanism
- Upcoming PSC Partners Seeking a Cure Meetings:
  - PSC Community Meetup: Sunday, September 29, 2019 in Toronto, Canada; to educate and support Canadian patients and caregivers
  - 16<sup>th</sup> Annual Patient/ Caregiver Conference: Friday, April 24 – Sunday, April 26, 2020 in Denver, CO in collaboration with the University of Colorado Health and Children's Hospital Colorado; provides updates on the latest research on treatments, medications, procedures, and disease outlook
  - Patient-Focused Drug Development Meeting: Friday, October 23, 2020 in Washington, DC area; patients will share stories and unmet needs

## Discussion

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1. Regarding the new ICD-10 code for PSC, what proportion of the true patient population across the US does the data represent (based on the new code)?

The data presented is based on US insurance claims utilizing the new ICD-10 code. Komodo Health tracks K83.01 usage through insurance claims nationally; they indicated that the code is being used for approximately 70-80% of US insurance claims. The largest group not included in the study are patients from Department of Veterans Affairs facilities.

2. Considering that ALP and ALT levels can vary significantly over a short period of time, in the absence of cholangitis, how should these fluctuations be addressed in clinical trials?

The use of multiple baseline values for ALP and ALT are recommended. Patients can be excluded from clinical trials with sludge in the bile ducts or an episode of cholangitis. In addition, before the start of a trial an external DILI committee should be created to address challenges related to ALP and ALT.

One participant noted that multiple baseline values may increase the screen failure rate. However, rescreening can allow the patient to be included as a suitable participant for the trial in the future. Screen failure rates are a challenge for recruitment in rare diseases. Additionally, requiring multiple baseline values and rescreening may pose further challenges for recruiting. To address these challenges, a suggestion was made to improve patient education about clinical trials, which could include a discussion of the need for multiple baseline tests, screen failures, etc.

3. Does the DILI criteria related to halting clinical trials apply to cirrhotic patients?

No, the criteria only applies to stable patients and should not be used for decompensated cirrhotics. However, this issue is being addressed in a new paper focused on cirrhotic and de-compensated cirrhotic patients across various clinical trials. It will include NASH, PSC, and other liver conditions.



4. What are the next steps going forward in the PRO development?

After gathering and analyzing input from all relevant stakeholders, such as the industry, the timeline to publication should be relatively short. A next step would then be to determine how to incorporate PROs into composite endpoints. The Forum will also reach out to clinical outcomes assessment experts from the FDA, to involve them in the article's publication.

5. Is there a way to validate the accuracy of the new ICD-10 code for PSC?  
Does the new ICD-10 code include pediatric patients?  
Are clinicians using the new ICD-10 code exclusively for PSC or is it also being applied more broadly by clinicians to episodes of cholangitis?

These questions will require verification from Komodo Health. Since the data is based on insurance claims, it likely includes both the adult and pediatric populations. To determine if the ICD-10 code is being appropriately applied to PSC patients instead of the wider cholangitis patient population, an independent chart validation would need to be conducted.

6. How will the PSC meta-analysis compliment or differ from the data in the *Gastroenterology* article from the IPSCSG?

The paper in *Gastroenterology* does not include any biochemistry data and has a limited impact on therapy. It is focused on a specialist center cohort of outcomes for patients living with PSC with hard endpoints and does not include risk scores.

7. Are the PSC PROs being considered for use in the pediatric population?

This is an important gap and will require some consideration for the best methods to collect and analyze this type of data. Parents or caregivers are likely to fill out PROs intended for children and adolescents; at this stage, there is hesitancy to gather this information in young children. There are also certain nuances in this population related to clinical trials, such as the focus on GGT rather than ALP. There's a spectrum of disease in pediatrics and young adults related to the autoimmune component of PSC. A better understanding of the role of GGT for DILI monitoring will also be useful. GGT can be elevated for a variety of reasons, including alcohol ingestion or other causes of enzyme induction.

8. Considering that about 80% of PSC patients have IBD, how accurate are PSC PROs in the context of confounding variables, such as IBD? Is there evidence of how well a PRO links to other measures of liver disease?

Preliminary comparisons of the PSC PRO in PSC patients with and without IBD indicated that there was not a significant difference between these cohorts. However, verifying that PROs reflect improvements in PSC and not a confounding condition is important. As a note, there are validated IBD PROs that are widely used in practice and clinical trials. There should also be an effort to standardize data collection from validated tools across certain autoimmune conditions, such as Colitis and Crohn's Disease. In the future, a study could examine which symptoms in a PSC tool are attributable to PSC or IBD. However, since the colon is integrally related to PSC, it may be difficult to separate out symptoms attributable to IBD and PSC.

One participant noted that a PRO should not be coordinated with biochemical data. The goal of a PRO is to measure the way the patient feels, functions and/ or survives in their daily life without interpretation of the patient's response by a clinician or other individuals. Therefore, attempting to correlate PROs with biochemical data would not be appropriate. However, other participants indicated that a therapy for PSC could be strengthened by linking the PRO to specific disease activity. Participants noted that PRO tools cannot be used in isolation. In pediatrics, the younger the patient, the less the association between disease severity in the colon and their symptoms.

9. What is the current state of science regarding the use of technology for electronic data collection in PSC studies?

This has been done in other disease areas, but not yet in PSC. There is a need to make data collection more convenient for patients without discarding the ability to provide information with pen and paper. In NASH wearables have been utilized to track activity and sleep. This is an opportunity in PSC. PROs could be collected online or from a handheld device, and this method is often used to monitor pruritis in clinical trials.

10. What are the biggest challenges in PSC clinical trials, considering issues such as enrollment, retention, attrition, etc.?

There is a need for better education of both investigators and patients about clinical trials, ineligibility for inclusion in studies due to fluctuating baseline data, and the number of screening failures. Patients should be aware of the total amount of time involved in entering a clinical trial and not just the length of time a therapy will be studied. Eligibility and enrollment are bigger issues in PSC trials than retention. To minimize the burden of trial participation, remote visits could be utilized; this would allow blood to be taken and sent to a central lab for processing. However, in the United States remote visits involve a number of issues, such as financial considerations and potential liability, and are unlikely to be utilized.

**Comments**

- Investigators were encouraged to submit clinical outcome measures to the FDA earlier to alleviate some of the burden of having to revise it (if requested by the FDA).
- When discussing PROs there is a distinction about whether they are being used for labeling, reporting or endpoints.

## SESSION II: PSC REGULATORY & TRIAL UPDATES

### PSC Regulatory Updates (EMA)

**Presenter:** Elmer Schabel, *European Medicines Agency (EMA)*

**Slides:** [https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P6\\_2019-PSC-Forum-3\\_Schabel.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P6_2019-PSC-Forum-3_Schabel.pdf)

- EMA published a reflection paper in 2018 on non-infectious liver diseases, including PSC
- EMA held a stakeholder meeting in December 2018. The reflection paper was then open for a comment period to allow stakeholders to make proposals for revisions and improvements.
- EMA received comments from 19 different organizations, with 11 of these comments relating to PSC.

- General comments suggested dividing the guidance into more specific, disease focused documents. The terms small duct and dominant strictures were considered not well defined and were suggested to be abandoned or modified.
- Comments Regarding Inclusion/ Exclusion Criteria and Population to be Studied- discussions centered around:
  - Population should allow occurrence of relevant clinical events
  - Diagnosis of disease should be clinical (imaging and biomarkers)
  - Fluctuating biochemistry and cholangitis flares complicate inclusion
  - Trade-off between “too early” population and “too late” population
  - Trade-off between patients with advanced fibrosis without relevant bile duct stenosis and the effect on fibrosis best shown in F3/ F4 patients
  - “Enrichment” of population with high ALP may be a way forward
  - Inclusion of IBD patients should depend on the mechanism of action (MOA)
  - In early trials, a mixed population may be acceptable (autoimmune hepatitis overlap (AIH))
  - Stop of ursodeoxycholic acid (UDCA) medication should not be required
- Comments Regarding Endpoints
  - Criticism for focusing too much on ALP and histology
    - ALP is an acceptable inclusion tool and stratification factor; role as surrogate needs clarifying
  - Non-invasive liver stiffness measure could be an alternative
  - PROs should be part of any PSC trials (adults and children)
  - Data sharing on natural history studies and placebo-treated patients should be encouraged
  - Adequate powering of studies is difficult due to low prevalence and heterogeneity of disease
  - The “totality of data” review approach may be best
  - Prevention of fibrosis progression/manifestation of cirrhosis (or its reversal) could be a surrogate
  - Regarding children, overlap (e.g., PSC-AIH) is more relevant and GGT is a reasonable surrogate
- Reflection Paper Summary: Trial Design and Endpoints
  - There is opportunity to utilize a strategy analogous to that used in NASH, with intermediate surrogate endpoints and confirmation of efficacy post-licensing. Co-primary endpoints based on histology and ALP reduction have been put forward, along with criteria for evaluation. There is also a need for non-invasive secondary endpoints, including biomarkers and imaging, as well as intermittent clinical events. The reflection paper also includes a recommendation on trial duration.
  - Criteria for evaluation: co-primary endpoints based on histology and ALP reduction with guidance given on how these should be evaluated; taken together these endpoints are considered robust and acceptable
  - Histological response: 1 stage reduction in fibrosis stage or no worsening of fibrosis (Nakanuma scoring system)
  - Serological response: reduction of ALP to 1.3x or 1.5x ULN, with 40% reduction
  - Confirmatory endpoints: combination of cirrhosis, model for end stage liver disease (MELD) >14; decomposition events and liver transplantation and death
  - Need for a set of non-invasive secondary endpoints (serum biomarkers and imaging) and intermittent clinical events (cholangitis, dominant stenosis, cancer)

- Trial duration: recommended 2 years for intermediate endpoint; up to 5 years for final evaluation; dependent on MOA and magnitude of effect
- Future Perspectives
  - All comments will be published with responses
  - Schedule to finalize paper is unclear but rough estimate are provided here
  - Discussion in the Gastroenterology Drafting Group: end of 2019
  - Discussion with relevant EMA groups and CHMP: further 3-4 months
  - Possible publication of final paper: 2<sup>nd</sup> – 3<sup>rd</sup> quarter of 2020

## PSC Regulatory Updates (FDA)

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**Presenter:** Ruby Mehta, *US Food and Drug Administration*

**Slides:** [https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P8\\_2019-PSC-Forum-3\\_Mehta.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P8_2019-PSC-Forum-3_Mehta.pdf)

- Annual PSC investigational new drug (IND) submissions: 1989-2019
  - Have been mostly be academic investigators
  - First commercial IND in 2012
  - Have increased a bit over time, with largest increases in 2010, 2014, and 2016
  - Commercial INDs have largely outnumbered academic submissions since 2014
- PSC IND Submissions:
  - There is currently no breakthrough therapy designation for PSC
  - One phase 3 trial is ongoing
  - Clinicaltrials.gov:
    - 168 PSC trials
    - 104 are clinical interventions
    - 23 pediatric trials
    - 10 trials in phase 3
      - 3 are actively recruiting
      - 1 is agreed upon with FDA
- Current Scientific Needs and Gaps
  - Largest need is understanding natural history of disease to better inform trial design (duration, sample size, endpoints) and to identify important characteristics of outcome variables (e.g., biochemical and imaging biomarkers, clinical benefit)
  - Data on performance of non-invasive biomarkers
  - To perform liver biopsy or document historical biopsy at enrollment for correlation purposes
- Endpoints for Phase 3 Trials:
  - For drugs that provide symptomatic improvement (e.g., pruritis, fatigue, etc.):
    - Regular approval pathway possible
    - Instruments/ scales should be developed early in drug development
    - Endpoints should be discussed early in drug development
    - Early statistical planning regarding how outcomes will be assessed

- For drugs with curative intent or for prevention of PSC progression:
  - Progression to cirrhosis for non-cirrhotic patients (enrichment is recommended)
  - Patients with compensated cirrhosis reach decompensation events, death, or liver transplant
  - Greater understanding of natural history, the time it takes a patient to progress from non-cirrhotic to cirrhosis or decompensation events
- Other biomarker endpoints: Magnetic resonance cholangiopancreatography (MRCP)
- Current biomarkers with limitations:
  - ALP
  - TB
  - ALT
  - GGT
  - Transient Elastography (FibroScan)
  - magnetic resonance elastography (MRE)
  - Other non-invasive biomarkers:
    - enhanced liver fibrosis (ELF)
    - N-terminal pro-collagen (PRO-C3)
    - FibroSure
- Role of liver biopsy; at baseline vs. at end of treatment vs. both
- Challenge to conducting phase 4 trial: recruitment and retention issues
- Natural History Comparators:
  - Limitations of using natural history data as comparators for phase 3 trials
    - Lack of rigor
    - Biases: sampling, recall, selection, information, reporting, risk of unmeasured confounders
    - Missing data and lack of quality control
    - Lack of internal validity
    - Safety cannot be assessed using historical data
    - How to get around multiple sources of bias and confounders?
  - Current Phase 3 Trial in PSC:
  - Double blind, placebo-controlled, randomized trial in non-cirrhotic subjects with PSC:
    - Same size ~ 400 subjects
    - Duration: 96 weeks
    - Primary endpoint: progression of  $\geq 1$  stage fibrosis (Ludwig's classification)

## Current Status of PSC Trials

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**Presenter:** Keith Lindor, *Arizona State University*

**Slides:** [https://forumresearch.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P7\\_2019-PSC-Forum-3\\_Lindor.pdf](https://forumresearch.org/storage/documents/PSC_Forum/psc_forum_3/P7_2019-PSC-Forum-3_Lindor.pdf)

See slides for additional details.

- High dose URSO is useful for the treatment of PSC, but a randomized trial showed that it may be detrimental for improvement in clinical endpoints.

- ALP typically used as an endpoint.
- Simtuzumab study showed baseline ALP as a predictor of clinical outcomes

<b>Improvement</b>	<b>No Effect</b>	<b>Worsening</b>
<u>Nor UDCA</u> <sup>1</sup> (ALP)	<u>Xifaxan</u> <sup>2</sup> (ALP after 12 weeks)	<u>High dose UDCA</u> <sup>3</sup> (cirrhosis, varices, cholangiocarcinoma, liver transplant, or death)
<u>Fenofibrate</u> <sup>4</sup> (ALP)	<u>Simtuzumab</u> <sup>5</sup> (hepatic collagen)	
<u>Benzafibrate</u> <sup>6</sup> (ALP & ALT)	<u>Maralixibat</u> (liver tests, serum bile, pruritis)	
<u>Cilofexor</u> <sup>7</sup> (ALP at week 12)	<u>NGM282</u> <sup>8</sup> (ALP, C4, AST, serum bile acids)	
<u>Fecal microbiota transplant</u> microbiome changes may correlate with ALP change	<u>Cenicriviroc</u> (minimal change to ALP, results to be published)	
<u>Vancomycin</u> (ALP) (Mayo Clinic)	<u>Curcumin</u> <sup>9</sup> (ALP, bilirubin, CRP)	

**Table 1. Closed trials** of PSC therapeutic candidates resulting in improvement, no effect, or worsening of primary endpoints (indicated in parentheses). References indicated by superscript.

1. Trauner et al. (2016), International Liver Congress, Barcelona, abstract LB02
2. Tabibian et al. (2017), *American Journal of Therapeutics*
3. Lindor et al. (2009), *Hepatology*
4. Abdalla et al. (2019), *Clinical Research in Hepatology & Gastroenterology*
5. Muir et al. (2019), *Hepatology*
6. Mizuno et al. (2015), *Journal of Hepato-Biliary-Pancreatic Sciences*
7. Trauner et al. (2019), *Hepatology*
8. Hirschfield et al. (2019), *Journal of Hepatology*
9. Eaton et al. (2019). *J. Gastroenterology*

<u>Therapeutic Candidate</u>	<u>Endpoint(s)</u>	<u>Study Size &amp; Duration</u>	<u>Study Details or Preliminary Study Results</u>
Obeticholic acid	Biochemistries, FibroScan	N=75 for 24 weeks	ALP reduced at 24 weeks
Mitomycin C	Mayo Risk Score	N=130 for 2 years	ERCP up to 5/ year; PI moved; unsure if study is ongoing
Vidofludimus calcium	ALP	N=30 for 6 months	Open-label study
Vancomycin	Biochemistries; MRCP; liver tests	N=40 for 30 months	Placebo-controlled, randomized Study is ongoing (Stanford)
Antibiotic treatment	ALP; Mayo Risk Score; total bilirubin	N=124 (5 study meta-analysis)	Shah et al. (2019), <i>Seminars in Liver Diseases</i>
Vancomycin vs. metronidazole	Mayo Risk Score	N/A	vancomycin promising
Sulfasalazine	ALP	N=42 for 14 weeks	Placebo-controlled, randomized PSC, IBD patients
All-trans retinoic acid	ALP	N=20 for 6 months	
DURECT	ALP	N=40 for 28 days	Terminated due to poor enrollment
Berberine & UDCA	N/A	N=90 for 12 weeks	30 on placebo; 30 on each of 2 doses
Mesenchymal stem cell transplants	ALP	N=56 for 12 weeks	Open-label study of IV infusions

**Table 2. Recently open trials** of PSC therapeutic candidates. Primary endpoint(s), study size and duration, as well as study details or study preliminary results are indicated.

## Phase 3 Trial Endpoints

**Presenter:** Gideon Hirschfield, *University of Toronto*

**Slides:** [https://hivforum.org/storage/documents/PSC\\_Forum/psc\\_forum\\_3/P3\\_2019-PSC-Forum-3\\_Hirschfield.pdf](https://hivforum.org/storage/documents/PSC_Forum/psc_forum_3/P3_2019-PSC-Forum-3_Hirschfield.pdf)

- New drugs for PSC should address cholangitis, cirrhosis, colitis, and cancer
- Trivedi et al (in prep):
  - Patients in the NHS study in UK for 10 years:
    - Of 100 patients with UC alone after 10 years:
      - All-cause mortality: 18
      - Liver transplant or PSC-related death: 0
      - Colectomy: 10

- Colorectal cancer: 2
  - Of 100 patients with UC and PSC after 10 years:
    - All-cause mortality: 41
    - Liver transplant or PSC-related death: 23
    - Colectomy: 16
    - Colorectal cancer: 7
  - Of 100 patients with UC and PSC after 10 years (from time of PSC diagnosis):
    - All-cause mortality: 55
    - Liver transplant or PSC-related death: 31
    - Colectomy: 20
    - Colorectal cancer: 10
  - Proportion of first clinical events attributable to liver transplant, PSC-related death, cholangiocarcinoma, and non-PSC-related death:
    - Cause of death differs for aged 50+ vs. 40 and younger
    - Non-PSC deaths increase while liver transplant decreases with age
- Simtuzumab study:
  - Neither 75mg nor 125mg of Simtuzumab modifies serum alkaline phosphatase levels over 96 weeks (Trivedi et al, in prep)
- Studies on baseline ALP:
  - At baseline, ALP levels are highly variable, going from < ULN to > 3x upper limit of normal (Muir et al., *Hepatology*, 2019)
  - Baseline serum ALP associated with progression to cirrhosis and PSC-related clinical events (Trivedi et al., in prep)
  - Over the 96 weeks ALP is variable (11.5% medial per-patient coefficient of variation); changes from baseline to weeks 12, 24, or 48 are not prognostic (Trivedi et al., in prep)
  - Spontaneous reductions (to  $\leq 1.5x$  ULN;  $\geq 40\%$  relative reduction) in ALP from baseline occur after 48 and 96 weeks (Trivedi et al., in prep)
  - Serum ALP not influenced by fibrosis stage, UDCA treatment, IBD, extent of ductal involvement, history of ascending cholangitis (Trivedi et al., in prep)
  - One of few studies measuring ALP in same central lab for all studies (Trivedi et al., in prep)
- Persistent improvement in ALP levels to < 1.5 upper limit of normal is associated with increased survival (Al Mamari et al., 2013, *J. Hepatology*)
- Hazard ratio for reaching an endpoint of PSC-related death or liver transplant:
  - Is increased when ALP levels are in the 0.5 – 2.5x ULN range – both at diagnosis and 1 year later
  - Is decreased for patients whose ALP levels decreased significantly during the first year after diagnosis
  - In this cohort of 366 patients followed for a median of 100 months, the optimal cutoff for ALP is 1.3x ULN
  - de Vries et al. (2016), *Liver International*
- Reduction of ALP by  $\geq 40\%$  is associated with increased survival 10 years later (17-23 mg/ kg/ day), regardless of treatment with UDCA or placebo for 5 years (Lindström et al. 2013, *Clinical Gastroenterology and Hepatology*)



- Liver histology predicts PSC outcomes:
  - Ishak, Nakanuma, and Ludwig liver histology staging all associate with transplant-free survival and time to liver transplant, but not cirrhosis-related symptoms; Nakanuma staging has a larger hazard ratio than Ishak or Ludwig staging
  - Based on a univariate analysis of 64 patients with a median follow up of 112 months
  - De Vries et al. (2015) *J. Hepatology*
- Treatment with placebo or either 75 mg or 125 mg of simtuzumab, a monoclonal antibody directed against LOXL2, for 96 weeks did not differentially influence reduction in Ishak fibrosis stage, progression to cirrhosis, or frequency of clinical events (Muir et al. 2019, *Hepatology*)
- Changes in Ludwig fibrosis stage over 2 years (Bowlus et al.):
  - Fibrosis progression in 40%
  - Fibrosis regression in 24%
  - Progression to cirrhosis in 16%
  - Increased risk of event associated with:
    - More severe fibrosis at baseline
    - Worsening of fibrosis (by Ishak stage, collagen content, and  $\alpha$ -SMA)
    - Higher baseline ELF (and components) and serum ALP
    - Increases of ELF and liver stiffness, but not ALP
- ELF is a nonspecific marker of liver fibrosis
- Serum fibrosis markers (Bowlus et al.):
  - Less ELF is independently associated with more transplant-free survival
  - Based on retrospective analysis of ELF in 2 cohorts of patients with large duct PSC
  - Higher baseline ELF & ALP: associated with greater risk of events
  - Increases in ELF, but not ALP, is associated with increased events
- NGM282 for 12 weeks in PSC:
  - Inhibited new bile acid synthesis (reduction in C4)
  - Improved serum markers of fibrogenesis and liver injury (ELF & pro-C3; ALT & AST)
  - Did not significantly affect ALP
  - Decreased pro-C3/C3M ratio (indicative of collagen deposition that correlates with liver histology and clinical outcomes) regardless of NASH or PSC (pooled data)
  - Hirschfield et al. (2019), *J. Hepatology*
- TE (FibroScan):
  - Both baseline and rate of change of liver stiffness shown to be prognostic of outcomes
  - Limitations:
    - Operator inexperience
    - Large increase with inflammation/ acute episodes/ dominant strictures
    - Can be used in trials, but not rigorously used in clinical practice
- MRE:
  - Liver stiffness is strongly correlated with fibrosis stage
  - Liver stiffness > 4.5kPa significantly increases risk of hepatic decomposition
  - Eaton, et al. (2016), *J. Gastroenterology & Hepatology*
  - Limitations:
    - These results require validation (only study of MRE in PSC)
    - MRE has high cost and limited availability

- May be more accurate than TE and combined with MRCP in a single visit
- Prognostic models with the greatest utility in risk stratification and inclusion:
  - Mayo Clinic Model
  - King's College Model
  - Multicenter Model
  - Revised Mayo Model
  - Amsterdam-Oxford Model
  - PREsTo
- Oral vancomycin therapy (OVT) in children with PSC:
  - Groups:
    - OVT only
    - UDCA only
    - OVT after UDCA therapy
    - Neither (no treatment)
  - Disease progression was similar in all groups to 1 year
  - Adverse events did not differ by group
  - Deneau, et al., Abstract 182, 2018, AASLD
- Overall, liver biopsy is a good starting point for Phase 3 trial endpoints, but there will likely be a need for composites.

## Discussion

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1. Regarding the Phase 3 trial utilizing Ludwig staging, why was this strategy implemented instead of utilizing Ishak staging? Why was fibrosis chosen as an endpoint?

Fibrosis was chosen as an endpoint because it is the most solid endpoint with a link to clinical complications. Regarding staging methods, Nakanuma includes components that aren't routine, such as orcein staining, which is not well known to pathologists. Ludwig staging's predictability of clinical events is equivalent to other staging systems. Ishak was not chosen because a one stage reduction in Ishak is easier to achieve than in Ludwig and it may not be accepted as indicative of improvement.

2. Regarding progression vs. improvement in fibrosis, which would be considered from a regulatory standpoint as more or less clinically meaningful?

Both progression and improvement could be acceptable as primary endpoints; both outcomes are relevant on a population level.

3. What would be necessary for MRE or FibroScan to become an acceptable surrogate endpoint from a regulatory perspective?

First, there needs to be standardization to ensure reproducibility across sites. In addition, FibroScan is variable in clinical practice. If you measure it every 3 months, you can see changes for a number of different reasons. However, a well powered study over a sufficient duration, such as 2-3 years, could establish changes between placebo and treatment groups. A clinically meaningful difference would establish FibroScan as a powerful surrogate. Along these lines, a 2 year study is a big effort for sponsors and patients. However, biopsies may not be needed when validating against outcomes.

More data is needed to determine the precision and accuracy of the test. An alternative view is that the ability to utilize FibroScan results may depend on its ability to predict specific disease states currently best identifiable via histology. Regulators supported collecting as much data as possible to consider the implications for an invasive or non-invasive biomarker.

4. From a patient perspective, what would or would not be an attractive clinical trial?

Education and information are key to patient participation in clinical trials. Patients prefer information about clinical trials to come from their clinicians rather than industry. Patients have expressed the greatest interest in participating in registries and the need for PSC education during the first two-years after a PSC diagnosis. The more educated patients are the more engaged they become.

Additionally, patients may perceive a benefit from modified clinical trials, such as a handheld device providing medical illustration, life quality scores, and wearables tracking health outcomes. Patients should be involved early in protocol development. Patients also indicated that longer placebo-controlled trials of 10-15 years would be challenging.

A patient perspective on clinical trials includes preferences for the following:

- PROs
- pediatric arms
- further development of prognostic tools
- risk assessment tools
- expanded inclusion criteria (such as allowing patients to continue taking URSO)
- informing patients about trial results
- continued access to a drug following the trial

A related question explored whether patients with mild disease, would be interested in enrolling in a study. The panel noted that patients with mild disease do better and have a larger placebo effect.

In further discussion of pediatric trials, regulators indicated that they may be considered after there is animal data that establishes the prospect of a direct benefit and preliminary safety data in adult humans.

5. From a patient perspective, what are barriers to entering clinical trials?

The major barrier to trial participation is a time constraint, as related to taking time off work to visit the clinic, amount of time spent at the clinic per visit, and the number of clinic visits required by the study.

6. How can clinical trials improve the recruitment experience for patients?

It would be helpful to simplify the language in and limit the length of the informed consent documents. In addition, the consequences of consenting to trial participation should be made clear, including the length of the trial.

7. How can clinicians get their colleagues to refer patients for trials?

- Liver care is often provided by gastroenterologists in the community. One option is to utilize the society networks, such as AASLD, the American College of Gastroenterology (ACG) or the American Gastroenterological Association (AGA), to help recruit patients to trials. However,

practitioners and clinicians may be skeptical of a society leading specific charges to facilitate trials.

- A second option is to engage hepatologists and hepatology centers that may not focus on clinical trials. However, this could be perceived as detrimental to the livelihood of the community gastroenterologists.
- A third option is to utilize the Crohn's and Colitis Foundation to create a registry of trials and trial sites to be widely disseminated among the IBD community, which may enrich the PSC population in trials.

8. What would be the ideal enrollment criteria for a trial for patients without cirrhosis?

One option is to exclude patients based on: a) liver histology indicative of cirrhosis, including at screening or any historical evidence of cirrhosis; b) a platelet count below 150; and c) liver stiffness greater than 14.4kPa. In addition, for sub-part H, the endpoints should have a reasonable chance of showing success. Guidance suggests separating cirrhotics and non-cirrhotics.

9. How artificial should patient populations be in clinical trials? Should there be data on all patients that exist in real life?

Usually, there is not a need to have data on all patients that exist in real life. That may be best left to clinical practice by physicians. However, there is a need to use an enriched population that is non-cirrhotic, but additional studies in late stage patients are also needed.

10. How should UDCA be treated in clinical trials?

Since UDCA is widely used in PSC, patients should be stratified for its use in clinical trials. UDCA is a relative confounder in understanding the efficacy of therapies.