Landscape of Clinical Trials

Keith D. Lindor, MD
Senior Advisor to the University Provost – Arizona State University
PSC Liver Forum – September 2019
## PSC Clinical Trials – Closed (older)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Status</th>
<th>Recruiting</th>
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<tbody>
<tr>
<td>Ursodeoxycholic Acid</td>
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<td>Norursodeoxycholic Acid (NUC-3)</td>
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<td>A Pilot Study of Xifaxan</td>
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<td>Simtuzumab (GS-6624) in the Prevention of Progression of Liver Fibrosis</td>
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<td>Pilot Study of Fenofibrate</td>
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<td>Obeticholic Acid (OCA) (AESOP)</td>
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<td>A Trial of BTT1023 (BUTEO)</td>
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<td>Bezafibrate</td>
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<td>A Study Evaluating the Safety and Efficacy of Curcumin in Patients</td>
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<td>Phase 2 Study of NGM282 in Patients</td>
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<td>PERSEUS: Preliminary Efficacy and Safety of Cenicriviroc in Adult</td>
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<td>A Research Study to Evaluate Safety and Efficacy of DUR-928</td>
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<td>Fecal Transplant</td>
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<tr>
<td>Safety, Tolerability, and Efficacy of Cilofexor in Adults (PSC-Phase 3)</td>
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Studies Closed to Enrollment
Results – UDCA High Dose

Model Of All Primary Endpoints
Adjusted For Mayo Risk Score, Presence of Varices, and Stage

Nor Ursodeoxycholic Acid

- Dr. Falk Pharma GmbH
  - Double-blind
  - 159 patients, 2 years
  - 3 doses and placebo
  - Change in alkaline phosphatase
Relative Changes in ALP from Baseline to End of Treatment with nor-Urso

VALUES (%) ARE MEANS (SD)

- Placebo (N = 40) 1.2%
- NU 500mg (N = 39) p = 0.0029
  -12.3%
- NU 1000mg (N = 41) p = 0.0003
  -17.3%
- NU 1500mg (N = 39) p < 0.0001
  -26%

Serum alkaline phosphatase at baseline and after 12 weeks of rifaximin therapy - Xifaxan

Following 12 weeks of rifaximin therapy, there was no clinically or statistically significant change in the primary endpoint, serum alkaline phosphatase (p=0.47). The median serum alkaline phosphatase following 12 weeks of rifaximin therapy among individuals who completed the study (318 U/L) was also not significantly different from baseline value (i.e. per-protocol analysis, p=0.81).

FIG. 1. Mean change in hepatic collagen content. Figure shows mean hepatic collagen content at baseline, week 48, and week 96. $P$ values versus placebo are from a mixed effects model for repeated measures at week 96. $P$ values are change from baseline versus placebo from a mixed-effects model. *$P = 0.73$, †$P = 0.33$.

FIG. 3. PSC event-free survival by treatment group. Figure shows survival free of PSC-related clinical events by treatment group. \( P \) values are by stratified log-rank test. \( P \) value from stratified log-rank test. Abbreviation: SIM, simtuzumab.
PSC Event-Free Survival by baseline ALP, baseline ELF score & change in ELF Score at week 12 - Simtuzumab

*Survival free of PSC-related clinical events by baseline ALP tertile.

Trajectory of Serum Alkaline Phosphatase in PSC treated with Fenofibrate

**ALP**

![Graph showing the trajectory of Serum Alkaline Phosphatase (ALP) in PSC treated with Fenofibrate](image)

Open Label Study of Maralixibat in the Treatment of Itching in PSC

- 27 Patients
- No real change in liver tests or serum bile acid level
- No change in pruritus
Obeticholic Acid

- Intercept Pharmaceuticals
  (currently recruiting patients)
  - Multicenter
  - 75 patients, 24 weeks
  - Biochemistries, fibroscan
Obeticholic Acid for the Treatment of Patients with PSC - Results

<table>
<thead>
<tr>
<th>(U/L)</th>
<th>Placebo (N = 25)</th>
<th>OCA 1.5-3 mg (N = 25)</th>
<th>OCA 5-10 mg (n = 26)</th>
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<tr>
<td>Mean Baseline ALP</td>
<td>563</td>
<td>423</td>
<td>429</td>
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<tr>
<td>Mean Change from Baseline in ALP at Week 12</td>
<td>-53</td>
<td>-57</td>
<td>-135*</td>
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<tr>
<td>Mean Change from Baseline in ALP at Week 24</td>
<td>-27</td>
<td>-105</td>
<td>-110*†</td>
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<tr>
<td>Mean Percentage from Baseline at Week 24</td>
<td>+1%</td>
<td>-22%*</td>
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*p<0.05
† Primary endpoint was ALP change for OCA 5-10 mg compared to placebo at week 24
Use of BTT1023 (Timolumab), in the treatment of patients with PSC (BUTEO)

- Open label
- 59 patients
- Alkaline phosphatase improvement as endpoint
- Originally to end 2015, now closed Oct 2018
Bezafibrate

Changes in Liver Function Tests

Solid line indicates trend of alkaline phosphatase (ALP)
Dashed line indicates trend of alanine aminotransferase (ALT).

P <0.01
** P <0.05 compared with week 12 by Wilcoxon signed-rank test
† P < 0.01 compared with week 24 by Wilcoxon signed-rank test.

Cilofexor Improves Serum ALP in Patients with PSC

**FIG. 1.** Cilofexor improves serum ALP in patients with PSC. (A) Median (IQR) serum ALP between baseline and week 12 of the double-blind phase of the study. (B) Median absolute change in serum ALP from baseline to week 12 of therapy. P values versus placebo are according to Wilcoxon rank-sum test. (C) Median (IQR) change in serum ALP relative to the ULN between baseline and week 12 of therapy. (D) Median relative (percentage) change in serum ALP from baseline to week 12 of therapy (overall and according to UDCA treatment). P values versus placebo are according to Wilcoxon rank-sum test.

Effect of Cilofexor on Liver Biochemistry & Markers of Fibrosis & Bile Acid Homeostasis

*Cilofexor 100 mg leads to improvement of serum GGT, ALT, AST & TIMP-1 compared with placebo. P values for cilofexor 100 mg versus placebo are according to Wilcoxon rank-sum test.

Individual Changes in Total Bilirubin Before & After Treatment - Curcumin

Individual Changes in C-Reactive Protein Before & After Treatment - Curcumin


* Available for 14/15 subjects
Effect of NGM282, an FGF19 analogue

Effect of NGM282, an FGF19 analogue


Fig. 2. Key outcome measures. (A) Serum levels of ALP at baseline and week 12. (B) Serum levels of C4 at baseline and week 12. (C) Serum levels of total endogenous bile acids at baseline and week 12. (D) Change in ALT from baseline over time. (E) Change in AST from baseline over time. All data are mean ± SEM. Statistical tests were ANCOVA (panels A-C) or mixed-effect model repeated measures (panels D-E) analyses. *p < 0.05, **p < 0.01, ***p < 0.001. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; EOT, end of treatment at week 12.
Macrophages contribute to the pathogenesis of sclerosing cholangitis in mice - Cenicriviroc

**HIGHLIGHTS:**
- Peribiliary macrophages are increased in PSC and animal models of PSC.
- Both M1-like and M2-like peribiliary macrophages are increased.
- Genetic & pharmacologic CCR2 inhibition restrains monocyte recruitment.
- CCR2 inhibition reduces fibrosis & cholestasis in animal models of PSC.
- These studies support the use of CCR2 inhibitors in human PSC.

Cenicriviroc in Adult Participants with PSC

- 24 patients, is complete
- Minimal change in alkaline phosphatase (4.5% drop)
- Not published yet
Fecal Microbiota Transplant

- 10 Patients, all with IBD & PSC
- 30% had ≥ 50% decrease in ALP
- Microbiome changes may correlate with ALP change
Studies Still Enrolling
Mitomycin C Therapy for Patients with PSC

- 130 patients, randomized study, 2 yrs, drug given at ERCP (up to 5x per year)
- Mayo risk score as endpoint
DHODH Inhibition Leads to Metabolic Stress in Activated Cells – Vidofludimus Calicum

**Lymphocyte**
- Metabolically silent
- DHODH is functionally not important

**Activated Lymphocyte**
- DHODH↑
- Rate limiting step in pyrimidine synthesis

**Stressed Lymphocyte**
- IMU-838 triggering:
  - Pyrimidine pool↓
  - Metabolic stress signals↑

**Pharmacological Effects**
- Block of transcriptional Elongation
- Blocking Tr17 / Tr1 Cytokine Release
- HEXIM1 Translocation
- Apoptotic gene transcript stabilization
- Apoptosis

3 days


SOURCE: https://www.immunic-therapeutics.com/imu-838/
Vidofludimus Calicum

- NIH sponsored, open label
- 30 patients, 6 month treatment
- Alkaline phosphatase as endpoints
Vancomycin

- **Stanford University** (study is ongoing)
  - 40 patients, 3 months
  - Biochemistries, MRCP, liver tests

- **Mayo Clinic** (study completed)
  - 35 patients, 12 weeks
  - Biochemistries and Mayo Risk Score
Effect of Antibiotic Treatment on ALP in PSC Patients

Forest plot showing the change in alkaline phosphatase (ALP) postantibiotic treatment in primary sclerosing cholangitis (PSC) patients ($I^2 = 44.93, p = 0.08$). CI, confidence interval.

Effect of Antibiotic Treatment on MRS in PSC Patients

Forest plot showing the change in Mayo PSC risk score (MRS) postantibiotic treatment in primary sclerosing cholangitis (PSC) patients ($I^2 = 47.60$, $p = 0.06$). CI, confidence interval.

Vancomycin & Metronidazole

Mean Difference of PSC Mayo Risk Score in Vancomycin & Placebo Groups

Sulfasalazine for the Treatment of PSC

- 42 participants, 14 weeks
- Placebo controlled, randomized
- Alkaline phosphatase endpoints
- All have IBD
- Multicenter
All-trans Retinoic Acid - PSC

- 20 patients, open label
- 6 months
- Alkaline phosphatase endpoint
Durect – PSC

• 40 patients, randomized
• 28 days
• Alkaline phosphatase endpoint
• Terminated due to poor enrollment
Hightide – Berberine – UDCA - PSC

• 90 patients
• 30 patients on each of 2 doses
• 30 patients on placebo
• 12 weeks dose finding
Mesenchymal Stem Cell - PSC

- 56 patients, open label
- IV infusion
- 2 weeks
- Alkaline phosphatase endpoint
Promising Approaches

- Nor Ursodeoxycholic Acid
- Obeticholic Acid
- Bezafibrate
- Fecal Transplant
- (NGM282)
- Vancomycin
- New Drugs in Pipeline
## PSC Clinical Trials - Open

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Conclusion

• Many drugs have been tested
• Different mechanisms
• Some studies adverse results
• Several studies actively recruiting
THANK YOU!