Phase 3 Trial Endpoints

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Phase 3 Trial Endpoints

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"If it looks good, you'll see it. If it sounds right, you'll feel it. If it's marketed right, you'll buy it. But...if it's real, you'll feel it." – Kid Rock "Let's rock on."
Hepatologists keep trying to leave UDCA zone..

- “UDCA does work; the trials are just wrong”
- “We all know the trial is not going to be positive’
- “We can’t take part in that trial because patients won’t agree to biopsies…”
- “But clearly the disease is a consequence of xx so you can’t treat with…”
- “I believe in early adoption as it is obvious yy works…”
- “What is the pathway to approval?”
The proportion of first clinical events attributable to liver transplantation, PSC-related death, cholangiocarcinoma and non-PSC-related death

Chi square = 181.0; P<0.001

Clinical event key
- Red: Non-PSC-related deaths
- White: Cholangiocarcinoma
- Blue: Liver transplants
- Diagonal: PSC-related deaths

Age strata at PSC diagnosis (yrs.)
- 18-30: 100/552
- 31-40: 96/291
- 41-50: 111/323
- 51-60: 163/417
- >60: 337/770

Trivedi et al. In Prep.
Survival in PSC and serum ALP values

End points

SAP persistent improvement to <1.5 ULN

No persistent improvement of SAP to <1.5 ULN

$p < 0.0001$

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
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</thead>
<tbody>
<tr>
<td>Group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No SAP improvement to &lt;1.5 ULN</td>
<td>84</td>
<td>60</td>
<td>29</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>0</td>
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<tr>
<td>SAP improvement to &lt;1.5 ULN</td>
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<tr>
<td></td>
<td>55</td>
<td>46</td>
<td>22</td>
<td>12</td>
<td>5</td>
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<td>0</td>
</tr>
</tbody>
</table>

Journal of Hepatology 2013; 58:329-334
• Retrospective study, 366 patients with PSC were followed for a median of 100 months (67,150)
  - 66 (18%) had an outcome of PSC related death or liver transplant

• Hazard ratio increased with increasing ALP in a range from 0.5-2.5xULN at both T0 (Fig A) and T1 (Fig B), and patients with a reduction in ALP from T0 to T1 also had a reduction in hazard ratio (Fig C)
  - In this cohort of patients the optimal cutoff was found to be ALP <1.3xULN
Predictive value of ALP and outcome
Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis

198 patients enrolled in the 5-year Scandinavian UDCA trial in 1996 randomized to UDCA vs placebo with extended follow-up

UDCA-treated patients with a biochemical response (ie, normal or ≥40% reduction in ALP after 1 year in the trial) vs nonresponders

Biochemical responders vs nonresponders, regardless of treatment with UDCA (P = .0001, log-rank test)
Serum ALP in SIM study

Baseline ALP

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;ULN</td>
<td>7</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>77</td>
</tr>
<tr>
<td>&gt;1.5x ULN</td>
<td>145</td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>121</td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>30</td>
</tr>
</tbody>
</table>

No Effect of SIM on Serum ALP

- Baseline ALP:
  - No Effect of SIM on Serum ALP

- Median ALP, U/L (Q1, Q3):
  - SIM 125 mg
  - SIM 75 mg
  - Placebo

Spontaneous Reductions in Serum ALP

ALP Reduction to ≤1.5x ULN

<table>
<thead>
<tr>
<th></th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5x ULN</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>2</td>
<td>4</td>
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</table>

≥40% Relative Reduction

<table>
<thead>
<tr>
<th></th>
<th>Week 48</th>
<th>Week 96</th>
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</thead>
<tbody>
<tr>
<td>&lt;ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>&gt;1.5x ULN</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>&gt;2x ULN</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

Trivedi et al. In Prep.
Serum ALP is Widely Variable

- Overall, ALP did not change between baseline and Wk 96
- Median per-patient CV was 11.5% (IQR 8.9, 14.2), but varied widely

Trivedi et al. In Prep.
Impact of Baseline Factors on ALP Variability

Variability in serum ALP was not influenced by baseline ALP, fibrosis stage, UDCA treatment, IBD phenotype, extent of ductal involvement, history of ascending cholangitis, or treatment arm

* Data for study interval Wk 0–12.
Prognostic Utility of Serum ALP

Baseline serum ALP was associated with:
- Progression to cirrhosis (OR per 10-U/L: 1.02; 95% CI 1.00, 1.03)
- PSC-related clinical events (HR per 10-U/L: 1.02; 95% CI 1.01, 1.02)

Changes in serum ALP from baseline to Wk 12, 24, and 48 were not prognostic.

CI, confidence interval; OR, odds ratio; HR, hazard ratio.

Trivedi et al. In Prep.
Liver histology and PSC outcome

- 4 observational publications with long-term follow-up comprising 826 cases demonstrated that Ludwig stage was independently associated with death/LTx.
- de Vries et al. assessed the prognostic value of Ludwig, Ishak, and Nakanuma scoring systems in 64 patients with PSC with a median follow up of 112 months.
  - Outcomes included PSC related death, PSC related malignancies, LTx and cirrhosis-related symptoms.
  - In univariate analysis, Ishak, Nakanuma and Ludwig stage all associated with transplant free survival and time to liver transplant but not cirrhosis related symptoms (Nakanuma KM Shown below).
  - Nakanuma staging had a larger hazard ratio than Ishak/Ludwig.

A B

A: Transplant-free survival

- Stage 1 (n = 2)
- Stage 2 (n = 43)
- Stage 3 (n = 12)
- Stage 4 (n = 1)

Follow-up time (months)

B: Liver transplantation

- Stage 1 (n = 2)
- Stage 2 (n = 43)
- Stage 3 (n = 12)
- Stage 4 (n = 1)

Follow-up time (months)

p < 0.001, log rank

Muir et al. 2019

Bar chart showing the percentage of patients in different treatment groups:

- SIM 75 mg (n=77): 34% Worse, 32% No change, 34% Improved
- SIM 125 mg (n=67): 33% Worse, 31% No change, 36% Improved
- Placebo (n=72): 44% Worse, 33% No change, 22% Improved

Significance levels: p=0.12 for SIM 75 mg vs. placebo, p=0.13 for SIM 125 mg vs. placebo.

Muir et al. 2019
Changes in Ludwig Fibrosis Stage

<table>
<thead>
<tr>
<th>Baseline</th>
<th>n (%)</th>
<th>F0 n=14</th>
<th>F1 n=43</th>
<th>F2 n=39</th>
<th>F3 n=49</th>
<th>F4 n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 n=17</td>
<td></td>
<td>6 (35)</td>
<td>9 (53)</td>
<td>2 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F1 n=34</td>
<td></td>
<td>5 (15)</td>
<td>12 (35)</td>
<td>12 (35)</td>
<td>3 (9)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>F2 n=48</td>
<td></td>
<td>2 (4)</td>
<td>14 (29)</td>
<td>13 (27)</td>
<td>16 (33)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>F3 n=74</td>
<td></td>
<td>1 (1)</td>
<td>8 (11)</td>
<td>12 (16)</td>
<td>30 (41)</td>
<td>23 (31)</td>
</tr>
</tbody>
</table>

- Fibrosis progression in 40% and fibrosis regression in 24% between baseline and Week 96
  - Progression to cirrhosis in 16%

Bowlus et al.
## Associations Between Histologic Features and Disease Progression

*Separate multivariate models run with baseline and change from baseline for each variable. Hazard ratios for changes from baseline adjusted for baseline value.*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage F2–3 vs F0–1</td>
<td>4.13</td>
<td>1.77, 9.64</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-worsening vs worsening</td>
<td>0.31</td>
<td>0.18, 0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Improvement vs no change/worsening</td>
<td>0.04</td>
<td>0.01, 0.31</td>
<td>0.002</td>
</tr>
<tr>
<td>Hepatic collagen (baseline), per 1%</td>
<td>1.09</td>
<td>1.03, 1.16</td>
<td>0.006</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.14</td>
<td>1.10, 1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α-SMA expression (baseline), per 1%</td>
<td>1.15</td>
<td>1.07, 1.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.05</td>
<td>1.04, 1.07</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Increased risk of events associated with:
  - More severe fibrosis at baseline (F2–3; greater collagen and α-SMA expression)
  - Worsening of fibrosis (by Ishak stage, collagen content, α-SMA)

Bowlus et al.
F2-3 Fibrosis and Greater Hepatic Collagen Associate with Increased Risk of Disease Progression

Log-rank test p=0.0004
Log-rank test p=0.0103

Fibrosis Stage
Hepatic Collagen

Event-Free Survival, %

Time, mo

F0–1
F2–3

≤3%
3–5.6%
>5.6%

N at risk
(Events)

Fibrosis Stage
Hepatic Collagen

Bowlus et al. 19
Non-Worsening of Fibrosis Is Associated with a Reduced Incidence of Disease Progression

P-values by Fisher’s exact test.

Week 48

- Non-worse: 21% (26/125)
- Worse: 44% (27/62)

Week 96

- Non-worse: 15% (15/103)
- Worse: 49% (34/70)

Bowlus et al. 20
Vesterhus et al. performed a retrospective analysis of ELF on two cohorts of patients with large duct PSC

- Cohort 1: N=167, Median follow up of 4 years; Serum collected 1992-2006
- Cohort 2: N=138, Median follow up of 2.2 years; serum collected 2008-2012
- Actual tertile values not provided, but Youdon Index values were at 11.1 and 11.2 for the respective cohorts
- In multivariate cox regression ELF (and also Mayo Score) showed independent association with transplant free survival in both cohorts of patients

## Association Between ELF and Disease Progression

### ELF (Baseline)

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>ELF &lt;9.8</th>
<th>ELF ≥9.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>135 (0)</td>
<td>132 (3)</td>
</tr>
<tr>
<td>6-12</td>
<td>129 (3)</td>
<td>123 (3)</td>
</tr>
<tr>
<td>12-18</td>
<td>113 (12)</td>
<td>108 (14)</td>
</tr>
<tr>
<td>18-24</td>
<td>106 (15)</td>
<td>105 (16)</td>
</tr>
<tr>
<td>24-30</td>
<td>2 (22)</td>
<td>1 (22)</td>
</tr>
<tr>
<td></td>
<td>0 (22)</td>
<td>0 (22)</td>
</tr>
</tbody>
</table>

- Log-rank test p <0.0001

### ELF (Change from Baseline)

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>ELF increase &lt;0.20</th>
<th>ELF increase ≥0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>104 (0)</td>
<td>98 (6)</td>
</tr>
<tr>
<td>6-12</td>
<td>94 (7)</td>
<td>89 (8)</td>
</tr>
<tr>
<td>12-18</td>
<td>76 (18)</td>
<td>72 (19)</td>
</tr>
<tr>
<td>18-24</td>
<td>72 (19)</td>
<td>71 (20)</td>
</tr>
<tr>
<td>24-30</td>
<td>2 (22)</td>
<td>1 (22)</td>
</tr>
<tr>
<td></td>
<td>0 (22)</td>
<td>0 (22)</td>
</tr>
</tbody>
</table>

- Log-rank test p =0.1032

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Bowlus et al.
Associations Between Fibrosis Markers, ALP, and Disease Progression

- Increased risk of events with:
  - Higher baseline ELF (and components) and serum ALP
  - Increases of ELF and liver stiffness, but not serum ALP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELF (baseline), per 0.5-units</td>
<td>1.34</td>
<td>1.21, 1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.36</td>
<td>1.17, 1.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMP-1 (baseline), per 50-ng/mL</td>
<td>1.31</td>
<td>1.20, 1.42</td>
<td>0.0000</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.16</td>
<td>1.07, 1.25</td>
<td>0.0004</td>
</tr>
<tr>
<td>PIII-NP (baseline), per 2.5-ng/mL</td>
<td>1.26</td>
<td>1.15, 1.38</td>
<td>0.0000</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.12</td>
<td>1.01, 1.25</td>
<td>0.0320</td>
</tr>
<tr>
<td>HA (baseline), per 50-ng/mL</td>
<td>1.13</td>
<td>1.07, 1.19</td>
<td>0.0000</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.15</td>
<td>1.06, 1.24</td>
<td>0.0005</td>
</tr>
<tr>
<td>LS by TE (baseline), per 1-kPa</td>
<td>1.02</td>
<td>0.99, 1.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.08</td>
<td>1.03, 1.13</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum ALP (baseline), per 100-U/L</td>
<td>1.19</td>
<td>1.10, 1.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.12</td>
<td>0.96, 1.31</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Separate multivariate models run with baseline and change from baseline for each variable.
Pro-C3 and ELF in the NGM282 study

A

B

C

Potential Biomarkers- Transient Elastography

The thresholds that predicted fibrosis stages F1, F2, F3, and F4 were 7.4, 8.6, 9.6, and 14.4 kPa (Figure A)

Evaluated Clinical outcomes in 168 patients with PSC with a mean follow up of 3.9 ± 1.9 years
23 (14%) experienced clinical outcomes
   11 liver transplantations, 6 deaths (2 from cholangiocarcinoma, 2 from hepatocellular carcinoma, and 1 from liver failure), 6 hepatic complications (3 cases of ascites, 2 cases of variceal bleeding, and 1 case of hepatic encephalopathy)
   Both baseline and rate of change in liver stiffness were shown to be prognostic of outcomes (Figure B/C)

TE has limitations: operator inexperience, large increase with inflammation/acute episodes/dominant strictures
Only 20 patients had biopsy info (F0, n=4; F1, n=3; F2, n=6, F3, n=3, F4, n=4); however, liver stiffness was still found to be strongly correlated with fibrosis stage (R=0.84, P< 0.001, Fig A).

Patients who had baseline liver stiffness >4.5kPa had significantly increased risk of hepatic decompensation (Fig B).

These results require further validation (this is the only paper on MRE in PSC).

MRE has high cost/limited availability but may be more accurate than TE and can be combined with MRCP in a single visit for more

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# Prognostic Models

<table>
<thead>
<tr>
<th>Mayo Clinic Model</th>
<th>King's College Model</th>
<th>Multicenter Model</th>
<th>Revised Mayo Model</th>
<th>Amsterdam-Oxford Model</th>
<th>PREsTo</th>
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<tbody>
<tr>
<td><strong>Predictors of Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
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</tr>
<tr>
<td>Bilirubin</td>
<td>Hepatomegaly</td>
<td>Bilirubin</td>
<td>Bilirubin</td>
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<td>Histologic stage</td>
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<td>Albumin</td>
<td>Albumin</td>
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<td>Splenomegaly</td>
<td>Splenomegaly</td>
<td>AST</td>
<td>AST</td>
<td>AST</td>
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<tr>
<td>IBD</td>
<td>Alkaline phosphatase</td>
<td>Variceal bleeding</td>
<td>Alkaline phosphatase</td>
<td>Alkaline phosphatase</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>Platelets</td>
<td>Platelets</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PSC subtype</td>
<td>Duration of PSC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sodium</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hemoglobin</td>
<td></td>
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</tbody>
</table>

Slide courtesy Cynthia Levy
# UK-PSC score

**AGE - AT DIAGNOSIS**

| 18 |

**BILIRUBIN - AT DIAGNOSIS** | Units | BILIRUBIN - AT YEAR 2 | Units |
<table>
<thead>
<tr>
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</tbody>
</table>

**ALBUMIN (A)/ g/l - AT DIAGNOSIS**

**PLATELETS (Plt) (×10⁹/l) - AT DIAGNOSIS**

**HAEMOGLOBIN (Hb) g/l - AT DIAGNOSIS**

**ALKALINE PHOSPHATASE (ALP) units/l - AT YEAR 2**

**ALKALINE PHOSPHATASE (ALP) units/l - ULN**

**DISEASE TYPE - AT DIAGNOSIS**

- No extra-hepatic disease
- Presence of extra hepatic disease

**VARICEAL BLEED?**

- No bleed by by year 2
- Variceal bleed by year 2

**SHORT-TERM RISK SCORE (RSGT) - CALCULATED AT DIAGNOSIS**

- Min. Data for Short-term Score Not Entered

**PREDICTED SURVIVAL RATE 2 YEARS (%)**

- Calculate 1 Year Survival
- Calculate 2 Year Survival

**LONG-TERM RISK SCORE (ROLT) - CALCULATED AT 2 YEARS POST DIAGNOSIS**

- Min. Data for Long-term Score Not Entered

**PREDICTED SURVIVAL RATE 5 YEARS (%)**

- Calculate 5 Year Survival
- Calculate 8 Year Survival
Clinical outcomes of oral vancomycin therapy in pediatric primary sclerosing cholangitis

Objective:
To assess whether oral vancomycin therapy (OVT) prevents adverse liver outcomes in children with PSC

Methods:
Multicenter analysis of the occurrence of portal hypertensive complications, dominant stricture interventions, or liver transplantation within 3 years of PSC diagnosis in children treated with ursodeoxycholic acid (UDCA), OVT only, OVT after a UDCA trial, or nothing

Conclusions:
We reported the largest cohort of children with PSC treated with OVT to date. Adverse outcomes occurred at similar rates regardless of treatment with OVT, UDCA, or nothing.

Deneau MR, et al., Abstract 182
Proving It Works…

**IPSCSG statement 2**
Alkaline phosphatase is widely recognized as a clinical measure of cholestasis. Currently, albeit not formally validated, it is regarded as a potential surrogate outcome parameter [EL 4, RG D]

**IPSCSG statement 4**
Liver histology has the potential to be a robust surrogate endpoint for clinical trials in PSC [EL2b, RG B]

**IPSCSG statement 5**
In the absence of a convincing single surrogate endpoint combining multiple endpoints is considered advisable and should be explored further [EL 5, RG D]

In early phase studies bloods alone are ok to show a drug may work

Liver biopsy is likely solid evidence a treatment works

The next drug will probably be shown to work by looking at a combination of endpoints alongside long term extension studies