Introduction

• Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are chronic, progressive liver diseases that cause bile-acid related deterioration of bile ducts and often lead to liver transplantation.1,2

• The most common symptoms of PBC and PSC include fatigue and pruritus, which may significantly impair quality of life.1,2

• The severity of pruritus can be measured with the Adult Itch Reported Outcome (ItchRO) tool, a worst itch numeric rating scale (NRS).

• Maralixibat (MRX), a selective inhibitor of the apical sodium-dependent bile acid transporter, is in clinical development for PBC and PSC.

• The Adult ItchRO tool was originally developed using qualitative methods and cognitive debriefing in patients with PBC, and was a secondary endpoint in two studies of MRX in PBC (CLARITY; NCT01904058) and PSC (CAMEO; NCT02061540).1,3

Aim

• To assess and validate the scoring and psychometric properties of the Adult ItchRO tool for pruritus in adult patients with cholestatic liver disease in a post hoc analysis of data from the CLARITY and CAMEO studies.

Methods

Study population

• CLARITY was a 13-week, randomized, double-blind, placebo-controlled study with an intention-to-treat sample of 66 patients with PBC.

• CAMEO was a 14-week, pilot, open-label study in 27 patients with PSC.

Adult ItchRO tool

• The Adult ItchRO tool was completed twice daily (morning [AM] and evening [PM]) using electronic (e-) diaries. Patients were asked to rate their worst itch from the time they went to bed until waking up (AM diary), and from waking up until the time of completion (PM diary).

• In the CLARITY study, the e-diaries were completed at screening, baseline, and Weeks 1, 2, 3, 4, 8, and 13; and in the CAMEO study, at screening, baseline, and Weeks 1, 2, 3, 4, 5, 6, 10, and 14.

• At each time point, the Adult ItchRO e-diary was completed daily for 7 days and the average of the daily worst rating during this period was calculated (7-day score).

Other numerical rating scales used to validate the Adult ItchRO tool

• For the Adult ItchRO tool included 5D-Itch Scale, PBC-40, Medical Outcomes Study (MOS)-Sleep Scale, and Patient Impression of Change in Itchiness (PIC-Itch).1,3

Psychometric validation

• Due to different study designs, analyses of the CLARITY and CAMEO studies were conducted separately.

• Exchangeability of the AM and PM items

• The exchangeability of patients’ AM and PM e-diaries during baseline week was investigated using a longitudinal mixed model.

• Assessment of score quality

• Concurrent validity for the Adult ItchRO scores was examined by calculating correlations between the Adult ItchRO and the 5D-Itch Scale total scores, the six domains of the PBC-40, and the six domains of the MOS-Sleep Scale.

• The test-retest reliability (TRR) of the Adult ItchRO scores was investigated by calculating the two-way random intraclass correlation coefficients (ICCs)2,4,5 using the scores from the week prior to baseline.

• Analysis of minimal clinically important change in the Adult ItchRO score

• Anchor-based estimates were generated for the PC study by calculating summaries of the change in Adult ItchRO scores from baseline to Week 13 within strata of patients’ PIC-Itch ratings.

• Empirical cumulative density function (CDF) curves were generated for the Adult ItchRO scores and were stratified by PIC-Itch ratings.

Concurrent validity

• The Pearson correlation coefficients for the Adult ItchRO and the 5D-Itch Scale scores, PBC-40 domains, and MOS-Sleep dimensions in patients with PBC and PSC are shown in Figures 3 and 4, respectively.

• The strongest association in both studies was with the 5D-Itch Scale total score (r = 0.59 [patients with PBC] and r = 0.95 [patients with PSC]).

• Correlations were found between the Adult ItchRO scores and other covariates, including the PBC-itch (r = 0.51 and 0.65, respectively), PBC-Estimation (r = 0.62 and 0.57, respectively), and MOS-Sleep disturbance (r = 0.40 and 0.60, respectively).

• Approximately 50% of patients with PBC (37/66) recorded that PIC-itch was ‘much better’ at Week 13 with an average decrease in the Adult ItchRO score of –5.09 (Table 2).

• Average Adult ItchRO change scores within the two PIC-itch categories that define the anchors for establishing meaningful change were ‘no change’ (M = –0.89) and ‘a little better’ (M = –0.23).

• The estimate for meaningful change in the Adult ItchRO score was –1.74 (i.e. the difference between –0.89 and –0.23).

Testing the minimal clinically important change

• CDF plots for change from baseline scores in the Adult ItchRO stratified by PIC-itch ratings (Figure 5) showed CDF curves were monotonically separated in the expected order (i.e. ‘much better’, ‘a little better’, and ‘no change’), indicating patients’ level of change in the Adult ItchRO scores within each of these groups tended to be distinct from the other groups defined by the PIC-itch.

• The Adult ItchRO is an 11-point scale, measured AM and PM, that has good psychometric properties.

• Scores from the measure showed satisfactory convergent validity with covariates, ability to distinguish between known groups, and strong TRR.

• Distribution-based approaches showed the measure could detect changes as small as 1 point, while the anchor-based estimate for meaningful change was –1.74.

• The Adult ItchRO was shown to be strongly correlated with the 5D-Itch Scale and demonstrated favorable correlations with other quality of life measures of emotion and sleep disturbance.

• The Adult ItchRO may be a suitable endpoint for clinical trials investigating potential treatments for patients with PBC and PSC.

Table 1. Number of patients in the CLARITY1 and CAMEO2 studies with change scores ≥ 2 SEMs at study endpoint

<table>
<thead>
<tr>
<th>Change Score</th>
<th>CLARITY Count</th>
<th>Percentage</th>
<th>CAMEO Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse</td>
<td>2</td>
<td>0.3%</td>
<td>3</td>
<td>1.1%</td>
</tr>
<tr>
<td>Better</td>
<td>10</td>
<td>1.5%</td>
<td>7</td>
<td>2.6%</td>
</tr>
<tr>
<td>A little better</td>
<td>10</td>
<td>1.5%</td>
<td>12</td>
<td>4.4%</td>
</tr>
<tr>
<td>No change</td>
<td>27</td>
<td>4.0%</td>
<td>27</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

Table 2. Description statistics for Adult ItchRO change scores at Week 13 (endpoint) stratified by the PIC-itch stratified by the PIC-itch

<table>
<thead>
<tr>
<th>PIC-itch</th>
<th>Adult ItchRO Score</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>1</td>
<td>27</td>
<td>–5.09</td>
<td>2.05</td>
<td>0.40</td>
<td>[–6.30, –3.88]</td>
</tr>
<tr>
<td>Better</td>
<td>2</td>
<td>10</td>
<td>–2.63</td>
<td>1.41</td>
<td>0.27</td>
<td>[–3.88, –1.38]</td>
</tr>
<tr>
<td>A little better</td>
<td>37</td>
<td>–5.09</td>
<td>2.05</td>
<td>0.40</td>
<td>[–6.30, –3.88]</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>2</td>
<td>27</td>
<td>–0.21</td>
<td>0.30</td>
<td>0.06</td>
<td>[–0.63, 0.21]</td>
</tr>
</tbody>
</table>

Table 3. Effect sizes for the Adult ItchRO stratified by PIC-itch at Week 13

<table>
<thead>
<tr>
<th>PIC-itch</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse</td>
<td>1.40</td>
</tr>
<tr>
<td>Better</td>
<td>0.40</td>
</tr>
<tr>
<td>A little better</td>
<td>0.40</td>
</tr>
<tr>
<td>No change</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Conclusion

• The Adult ItchRO is an 11-point scale, measured AM and PM, that has good psychometric properties.

• Scores from the measure showed satisfactory convergent validity with covariates, ability to distinguish between known groups, and strong TRR.

• Distribution-based approaches showed the measure could detect changes as small as 1 point, while the anchor-based estimate for meaningful change was –1.74.

• The Adult ItchRO was shown to be strongly correlated with the 5D-Itch Scale and demonstrated favorable correlations with other quality of life measures of emotion and sleep disturbance.

• The Adult ItchRO may be a suitable endpoint for clinical trials investigating potential treatments for patients with PBC and PSC.