Poster 571

Psychometric validation of the Itch Reported Outcome (ItchRO™) Observer assessment in pediatric patients with Alagille syndrome or progressive familial intrahepatic cholestasis

Daniel Serrano,[1] Martha Gauthier,[1] Magdalena Harrington,[2] Lisette Acevedo[3]

[1]Endpoint Outcomes, Boston, MA and Long Beach, CA, USA; [2]Shire, Lexington, MA, USA; [3]Shire, Lexington, MA, USA (current affiliation: Orexigen Therapeutics, Inc., La Jolla, CA, USA)

Disclosure: Research was funded by the sponsor, Shire Development LLC. M Harrington is an employee of Shire and owns stock or stock options. L Acevedo is a former employee of Shire. The following authors have received compensation for serving as consultants or speakers for, or they or the institutions they work for have received research support or royalties from, the companies or organizations indicated: L Acevedo (Shire); M Gauthier (Shire); D Serrano (Shire).

Scan code to receive PDF file of the poster or visit: www.shirecongressposters.com/751764

INTRODUCTION

- Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) are pediatric cholestatic liver diseases that commonly present with intractable pruritus (itchiness) in infancy or early childhood.[1–3]
- Two versions of the Itch Reported Outcome instrument (ItchRO™) have been developed in accordance with US Food and Drug Administration guidelines[4] to assess itch in pediatric patients.
  - ItchRO(Pt)™ is the self-reported version (suitable for completion by patients aged 9 years and older).
  - ItchRO(Obs)™ is the observer-reported version.
- Maralixibat chloride (SHP625, formerly LUM001) is a potent, selective, minimally absorbed competitive inhibitor of the apical sodium-dependent bile acid transporter,[5] and is being assessed in clinical studies of pediatric patients with ALGS and PFIC.
- To date, the psychometric performance of the ItchRO has not been assessed for use in pediatric clinical trials.

OBJECTIVE

- To assess the psychometric properties of the ItchRO(Obs), including test–retest reliability (TRTR), concurrent validity, known-groups validity and ability to detect meaningful change.

METHODS

Study population

- This analysis used data from three studies.
  - The ItchRO validation study (LUM1038; ClinicalTrials.gov identifier: NCT02131623): a 2-week, stand-alone, observational, non-interventional study of children with ALGS or PFIC.
    - For children aged 5–18 years, both the child and their caregiver participated.
    - For children under 5 years of age, only the caregiver participated.
  - IMAGO (LUM001-302; ClinicalTrials.gov identifier: NCT01903460): a 13-week, randomized, double-blind, placebo-controlled study of the safety and efficacy of maralixibat in children (aged 1–18 years) with ALGS.
    - Eligible patients had moderate-to-severe itching defined as a daily average score of at least 2 for item 1 of the ItchRO(Obs).
  - INDIGO (LUM001-501; ClinicalTrials.gov identifier: NCT02057718): a 72-week, open-label study of the efficacy and long-term safety of maralixibat in children (aged 1–18 years) with PFIC.
- Itch severity was not an eligibility criterion for enrollment in the validation and INDIGO studies.

ItchRO(Obs)

- In all studies, one caregiver for each patient completed an ItchRO(Obs) diary twice daily (morning and evening) (Table 1).
- The current study analysed the data for item 1 of the ItchRO(Obs), which assesses itch severity on a five-point scale (0 = no itch, 4 = most severe itch).
  - ItchRO(Obs) item 1 daily average scores were aggregated to generate 1-week, 2- week or 4-week mean scores.

Psychometric validation

- Table 1 summarizes the instruments used in this psychometric validation.

Test–retest reliability

- The TRTR was investigated by calculating the two-way, random intraclass correlation coefficients (ICCs)[6] for the 1-week mean ItchRO(Obs) daily average scores for week 1 relative to those for week 2.
  - Scores were pooled from the 2-week observation period of the validation study and first 2 weeks of screening of the INDIGO and IMAGO trials.
  - An ICC value in the range 0.7–0.8 was the minimum required to indicate sufficient TRTR.

Concurrent validity

- Pearson correlation coefficients were calculated to indicate the concurrent validity between the ItchRO(Obs) and Pediatric Quality of Life Inventory (PedsQL™) total and psychosocial and physical functioning domain scores.
  - Mean ItchRO(Obs) daily average scores and PedsQL scores were calculated for the 2-week observation period of the validation study.
  - In the IMAGO and INDIGO pooled analysis, mean ItchRO(Obs) daily average scores and PedsQL scores were calculated for the 4-week period preceding week 13.
- Pearson correlation coefficients were also calculated for mean ItchRO(Obs) daily average scores versus Itch Numeric Rating Scale (NRS) scores in the validation study.
- A Pearson correlation coefficient of 0.40 or higher was pre-specified as indicating acceptable concurrent validity.

Known-groups validity

- The 2-week mean ItchRO(Obs) daily average scores were calculated for each level of the Clinician Scratch Scale (CSS) at visit 1.
  - Data were pooled from the 2-week observation period of the validation study and first 2 weeks of screening of the INDIGO and IMAGO trials.
  - Effect sizes were obtained from a linear model; the pre-specified criterion for known-groups validity was an effect size of 0.10 or greater.

Minimal clinically important difference (MCID)

- The distribution-based MCID analysis estimated the change in 1-week mean ItchRO(Obs) daily average score from week 0 to week 13 for the pooled IMAGO and INDIGO data.
  - An MCID was defined as a change that exceeded 0.5 standard deviation (SD) from the mean.
- The anchor-based MCID analysis estimated the relationship between the change in 1-week mean ItchRO(Obs) daily average scores and Caregiver Impression of Change (CIC) scores from week 0 to week 13 for the pooled IMAGO and INDIGO data.
  - Effect sizes were obtained from a linear model in which the change in ItchRO(Obs) daily average score was the outcome and CIC level the predictor.

Table 1. Overview of instruments used in the psychometric validation of the Itch Reported Outcome (Observer).

Instrument	Scoring and domains	Time of administration; reporter	Analyses for which instrument was used
Itch Reported Outcome (Observer)	Observer-reported, 5-point scale (0 = no itch, 4 = most severe itch)	Validation study: twice daily for 2 weeks; caregivers Clinical trials: twice daily throughout (including screening); caregivers	TRTR Concurrent validity Known-groups validity Distribution-based MCID Anchor-based MCID
Pediatric Quality of Life Inventory	PedsQL™ total and domain (psychosocial health and physical functioning) scores are obtained by direct item summation	Validation study: screening (visit 1) and end of 2-week validation period (visit 2); caregivers and age-appropriate children Clinical trials: end of screening (day 28 in IMAGO and day 42 in INDIGO) and week 13; caregivers and age-appropriate children	Concurrent validity
Itch Numeric Rating Scale	Self- or observer-reported, 11-point scale (0 = no itching, 10 = worst itching imaginable)	Validation study: visits 1 and 2; all caregivers and children aged 9 years or older Clinical trials: not assessed	Concurrent validity
Clinician Scratch Scale	Clinician-administered, 5-point scale (0 = none, 4 = cutaneous mutilation, hemorrhage and scarring evident)	Validation study: visits 2; clinicians Clinical trials: all visits from baseline to week 13; clinicians	Known-groups validity
Caregiver Impression of Change	Self-administered, 7-point scale (1 = best outcome, 7 = worst outcome)	Validation study: visit 2; caregivers Clinical trials: week 13; caregivers	Anchor-based MCID

ItchRO(Obs), Itch Reported Outcome (Observer); MCID, minimal clinically important difference; TRTR, test–retest reliability.

Table 2. Itch Reported Outcome (Observer) test–retest reliability.

Period of measurement	N	Mean ItchRO(Obs) daily average score				ICC
		Minimum	Maximum	Mean	SD	
Week 1	62	0	3.64	2.13	0.99	0.95
Week 2	62	0	4.00	2.17	0.96	

ICC, intraclass correlation coefficient; ItchRO(Obs), Itch Reported Outcome (Observer); SD, standard deviation; TRTR, test–retest reliability.

RESULTS

Study population

- A total of 62 patients were eligible for the analysis.
  - Validation study: n = 23 (ALGS: n = 22; PFIC: n = 1); IMAGO: n = 19; INDIGO (interim analysis): n = 20.

TRTR

- The pooled ItchRO(Obs) daily average scores from the validation study and the IMAGO and INDIGO trials were similar at week 1 and week 2 (Table 2).
  - The ICC across the 1-week retest interval was 0.95.

Concurrent validity

- The Pearson correlation coefficients indicated that there were correlations between the mean ItchRO(Obs) daily average score and PedsQL total and subscale scores in the expected direction (negative) for the validation study and pooled IMAGO and INDIGO data (Table 3).
  - The magnitudes of all the correlations (range, –0.40 to –0.52) exceeded the pre-specified acceptability criterion.
- In the validation study, a strong positive correlation was observed between the mean ItchRO(Obs) daily average score and Itch NRS (Table 3).

Known-groups validity

- The 2-week mean ItchRO(Obs) daily average scores increased with increasing CSS-defined severity level (Table 4).
- Differences in CSS scores accounted for 34% of the variance in ItchRO(Obs) daily average scores.
  - The largest contribution to this variance was made by the significant difference between the CSS levels of 'none' versus 'scarring' (effect size = 0.188); the magnitude of this effect size met the pre-specified acceptability criterion (Table 4).

Table 3. Concurrent validity between Itch Reported Outcome (Observer) daily average score and Pediatric Quality of Life Inventory total and subscale scores and Itch Numeric Rating Scale scores.

Data source	Correlation with mean ItchRO(Obs) daily average score			
	PedsQL total score	PedsQL psychosocial score	PedsQL physical function score	Itch NRS
Validation study (week 2)	–0.49	–0.47	–0.40	0.92
Pooled IMAGO and INDIGO data (week 13)	–0.52	–0.43	–0.48	NA

Values indicate the Pearson's coefficient (*r*).
ItchRO(Obs), Itch Reported Outcome (Observer); NA, not assessed; NRS, Numeric Rating Scale; PedsQL, Pediatric Quality of Life Inventory.

Table 4. Clinician Scratch Scale-based known-groups validity.

CSS level	Comparison	2-week mean ItchRO(Obs) daily average score		β[a]	95% CI	*p* value	Effect size
		Effect group	Reference (scarring)				
None	None vs scarring	0.75	2.43	–1.68	–2.46, –0.90	< 0.0001	0.188
Rubbing	Rubbing vs scarring	0.38	2.43	–2.05	–3.23, –0.86	0.0011	0.116
Scratching	Scratching vs scarring	2.01	2.43	–0.42	–1.13, 0.29	0.2373	0.005
Abrasion	Abrasion vs scarring	2.44	2.43	0	–0.52, 0.53	0.9873	0.0

[a]Rate of change for the trend across CSS groups over time.
CI, confidence interval; CSS, Clinician Scratch Scale; ItchRO(Obs), Itch Reported Outcome (Observer).

Table 5. Anchor-based minimal clinically important differences according to Caregiver Impression of Change level.

CIC level	Comparison	ItchRO(Obs) daily average score N, change		β[a]	95% CI	*p* value	Effect size
		Effect group	Reference (best)				
Much better	Much better vs no change	6, –1.48	7, –0.44	–1.04	–1.68, –0.4	0.0024	0.189
Better	Better vs no change	8, –1.03	7, –0.44	–0.59	–1.19, 0	0.0500	0.059
A little better	A little better vs no change	10, –0.5	7, –0.44	–0.06	–0.63, 0.5	0.8211	0.0
A little worse	A little worse vs no change	2, 0.32	7, –0.44	0.76	–0.16, 1.68	0.1001	0.035
Much worse	Much worse vs no change	1, –1.36	7, –0.44	–0.92	–2.14, 0.31	0.1362	0.025

[a]β is the rate of change for the trend across CIC levels over time.
The CIC level 'worse' was observed for n = 1 participant who had a missing week 13 ItchRO(Obs) assessment; effect size was inestimable for this participant and no data are reported for the 'worse' vs no change' categories.
CI, confidence interval; CIC, Caregiver Impression of Change; ItchRO(Obs), Itch Reported Outcome (Observer).

Minimal clinically important differences

- In the distribution-based MCID analysis of pooled IMAGO and INDIGO data, the reduction in ItchRO(Obs) daily average score between week 0 and week 13 for the maralixibat 140 mg group exceeded one standard deviation (–0.83 points; 95% confidence interval: –1.59, –0.08; SD: 0.78; $p = 0.0321$).
- In the CIC-anchor-based MCID analysis, the only significant and meaningful change estimate was associated with the CIC level 'much better' (Table 5).

CONCLUSIONS

- **Despite a limited sample size, which necessitated the use of only classical test theory validation methods, evidence suggests that the ItchRO(Obs) daily average scores are reliable, valid, and sensitive to detecting meaningful change in itch-related behaviors.**
- **The TRTR for ItchRO(Obs) daily average score was consistently strong, as were the concurrent validity correlations with PedsQL and Itch NRS scores.**
- **Known-groups validity tests provided strong evidence supporting psychometric validity, with higher CSS severity levels being associated with higher ItchRO(Obs) daily average scores.**
- **The distribution- and anchor-based MCID estimates for the pooled IMAGO and INDIGO data indicated that the ItchRO(Obs) daily average scores can be used to detect meaningful change.**

REFERENCES

1. Alagille D *et al. J Pediatr* 1987;110:195–200.
2. Davit-Spraul A *et al. Orphanet J Rare Dis* 2009;4:1.
3. Emerick KM *et al. Hepatology* 1999;29:822–9.
4. US Department of Health and Human Services Food and Drug Administration. 2009. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf (Accessed 26 September 2016).
5. Keller B *et al.* Falk Symposium 194. 2014 (congress abstract 55). Available from: http://www.falk-foundation-symposia.org/uploads/tx_tocfpshoperw/FS194_Freiburg_2014_Abstracts_01.pdf (Accessed 1 September 2016).
6. Shrout PE *et al. Psychol Bull* 1979;86:420–8.

Disclosures

Under the direction of the authors, Elizabeth Gandhi, an employee of Oxford PharmaGenesis, Oxford, UK, provided writing assistance for this publication. Editorial assistance in formatting, copy editing, fact checking and proofreading was also provided by Oxford PharmaGenesis. Shire International GmbH provided funding to Oxford PharmaGenesis for support in writing and editing this poster.

Mobile and environmentally friendly e-posters

3 ways to access the poster

Send an SMS
Text 'Poster 751764'
to 43704

Access online
http://www.shirecongressposters.com/751764

Scan QR code

No personal information is stored – standard charges may apply