



Development of the Patient- and Observer-Reported PRUCISION Instruments to Assess Pruritus and Sleep Disturbance in Pediatric Patients with Cholestatic Liver Diseases

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ABSTRACT

Introduction: Understanding how patients experience their disease is a vital step in optimal disease management, and patient- and observer-reported outcome (PRO and ObsRO, respectively) measures can add important details to clinical information that is obtained as novel treatments are developed. Instruments that measure meaningful symptoms and impacts from the perspective of pediatric patients with cholestatic liver disease or their caregivers are needed. This study aimed to identify salient concepts in pediatric cholestatic liver disease, develop novel PRO and ObsRO instruments, and establish the instruments' content validity.

Methods: Relevant signs, symptoms, and impacts of cholestatic liver disease were

identified through a literature review, interviews with expert clinicians, and concept elicitation interviews with children and caregivers of children who had progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome, biliary atresia, or primary sclerosing cholangitis. Additional cognitive debriefing interviews with patients and caregivers were performed to ensure that participants could understand the instructions, questions, and response scales of the PRO and ObsRO instruments, with modifications made as necessary to improve comprehension and/or usability.

Results: A total of 36 interviews with patients and caregivers were conducted. Pruritus and sleep disturbance (e.g., difficulty falling or staying asleep due to itch) were identified as the most problematic symptom and significant impact, respectively, of the pediatric cholestatic liver diseases assessed. The ObsRO and PRO instruments, called PRUCISION, focus on these key disease features in the morning and evening. Several modifications were made to the draft instruments following cognitive interviews. The final PRUCISION PRO and ObsRO measures are designed as an electronic diary to be completed twice daily. The response scales include pictorial, verbal, and numeric scales.

Conclusion: Novel PRO and ObsRO PRUCISION instruments were created that evaluate the patient experience of cholestatic pruritus in children with PFIC and other

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cholestatic liver diseases. The content validity of the PRUCISION instruments is established.

PLAIN LANGUAGE SUMMARY

Bile, a greenish liquid that is made in the liver, is released into the gut to help digest food. In cholestatic liver disease (CLD), bile flow is interrupted, and bile can build up in the body. One potential effect of this buildup is pruritus, or itchiness of the skin, which can be so intense that it interferes with daily activities. In this study, interviews were done with doctors, patients, and their caregivers to develop new tools to evaluate the most impactful symptoms of CLD in children. After interviewing five doctors and 36 patients and caregivers, two questionnaires called PRUCISION were developed and refined. During this process, participants were first asked about the frequency, severity, duration, and impact of their or their child's symptoms; pruritus was identified as the most common and disruptive symptom associated with CLD, even interfering with sleep. Then, the wording of the questionnaires was modified to make them easier to understand, particularly for younger children. The researchers also had patients do a card-sorting task to ensure that they understood the picture-based responses used in the questionnaires. Finally, more details were added to the instructions for caregivers to more clearly define scratching behaviors. In summary, the questionnaires developed in this study include the perspective of the patient or their caregiver and may be useful to see if new treatments can impact the most prominent symptoms and impacts associated with CLD.

Keywords: Cholestasis; Outcome assessment; Caregivers; Patient-reported outcome measures

Key Summary Points

Pruritus is a debilitating symptom experienced by pediatric patients with cholestatic liver disease. Itching in this population is not alleviated by scratching, has a significant impact on daily functioning, and substantially disturbs patients' ability to sleep.

New patient-reported and observer-reported outcome measures were developed in this study to assess pruritus, sleep disturbance, and tiredness. These instruments can be used in clinical trials to evaluate the efficacy of novel treatments for children with cholestatic liver diseases.

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome, biliary atresia, and primary sclerosing cholangitis are rare, severe pediatric cholestatic liver diseases (CLDs) that typically progress to liver failure if left untreated [1–3]. Historically, medical treatments were primarily palliative (e.g., nutritional support, symptomatic treatment of extrahepatic features including pruritus) and/or unapproved by health regulatory agencies [1, 4, 5]. The exceptions are recently approved inhibitors of the ileal bile acid transporter, odevixibat and maralixibat. Odevixibat was approved in 2021 for treatment of PFIC in patients ≥ 6 months of age in the European Union and for the treatment of pruritus associated with PFIC in patients ≥ 3 months of age in the United States [6, 7]. Maralixibat was approved in 2021 in the United States for treatment of cholestatic pruritus in patients ≥ 1 year old with Alagille syndrome [8]. Surgical operations (e.g., partial surgical interruption of the enterohepatic circulation in the case of PFIC and Alagille syndrome, Kasai portoenterostomy in the case of

biliary atresia, and liver transplantation in general) are also used to treat these diseases [1, 4, 9, 10].

Patients with these CLDs may experience intense pruritus (e.g., itching with cutaneous mutilation that draws blood) [3, 11–14]. This can lead to sleep loss, mood changes such as increased irritability, and potentially reduced attention and/or ability to focus at school; cumulatively, these disruptions can greatly reduce quality of life [1, 3, 9, 14, 15]. Intractable pruritus may be so disruptive that patients can be referred for liver transplantation in the absence of liver failure [1, 9, 11].

In recent years, there has been an effort to understand patient perspectives of these diseases, including the key symptoms, burden, and potential benefits of treatment [16, 17]. These perspectives, or the perspective of caregivers who have direct knowledge about patients' condition-related behaviors, have been increasingly recognized as important to characterize since clinical perspectives or physiologic measures may not always capture aspects of the disease that are meaningful to patients. As such, patient-reported outcome or observer-reported outcome (PRO and ObsRO, respectively) measures can augment clinician perspectives about disease progression or improvement. Additionally, gaining a better understanding of how patients and caregivers experience disease may facilitate the development of novel treatments by providing patient-centric endpoints for use in clinical trials.

Regulatory and health outcomes research bodies have issued best-practice guidelines to standardize the development of new PRO/ObsRO instruments [18–21]. Such codified steps of development broadly fall into two categories: (1) eliciting concepts related to disease burden that are important to the patient population being studied (and that are representative for the patient population) through interviews or other methods, and (2) as new tools are developed, ensuring that patients or caregiver respondents understand them as intended.

The objective of this study was to develop PRO and ObsRO instruments for pediatric patients with CLDs and their caregivers that reflected the patient experience of CLD,

including the most salient symptoms and impacts. Here, an ObsRO instrument was developed in addition to a PRO instrument since many patients with CLDs are diagnosed in early childhood before they can self-report their symptoms and/or functional limitations [3, 12, 22].

METHODS

This was a qualitative, observational study to identify meaningful concepts of health among pediatric patients with CLDs and their caregivers and to establish content validity (i.e., the extent to which the developed instrument measured the concept[s] of interest). To this end, the most relevant signs, symptoms, and impacts were identified by conducting a literature review, interviewing expert clinicians, and interviewing patients and caregivers (Fig. 1). As a part of this process, cognitive debriefing interviews [23] were conducted with patients and caregivers to evaluate the comprehension and ease of use of the PRO or ObsRO questions, response options, and instructions.

The study protocol, informed consent language, recruitment material, and other supporting information were submitted to an independent institutional review board (New England Institutional Review Board, Newton, MA, USA) for approval prior to study initiation. In addition, this study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements.

Literature Review

A targeted literature review was performed via searches of PubMed, ScienceDirect, AccessMedicine[®], ClinicalTrials.gov, Cortellis[™], and PROQOLID[™] databases to identify relevant signs, symptoms, and impacts of PFIC and related pediatric CLDs, with a focus on cholestatic pruritus. An additional search was conducted to identify experiences reported by patients or patient groups outside of the published literature and formal scientific databases (e.g., patient blogs). Articles were excluded if

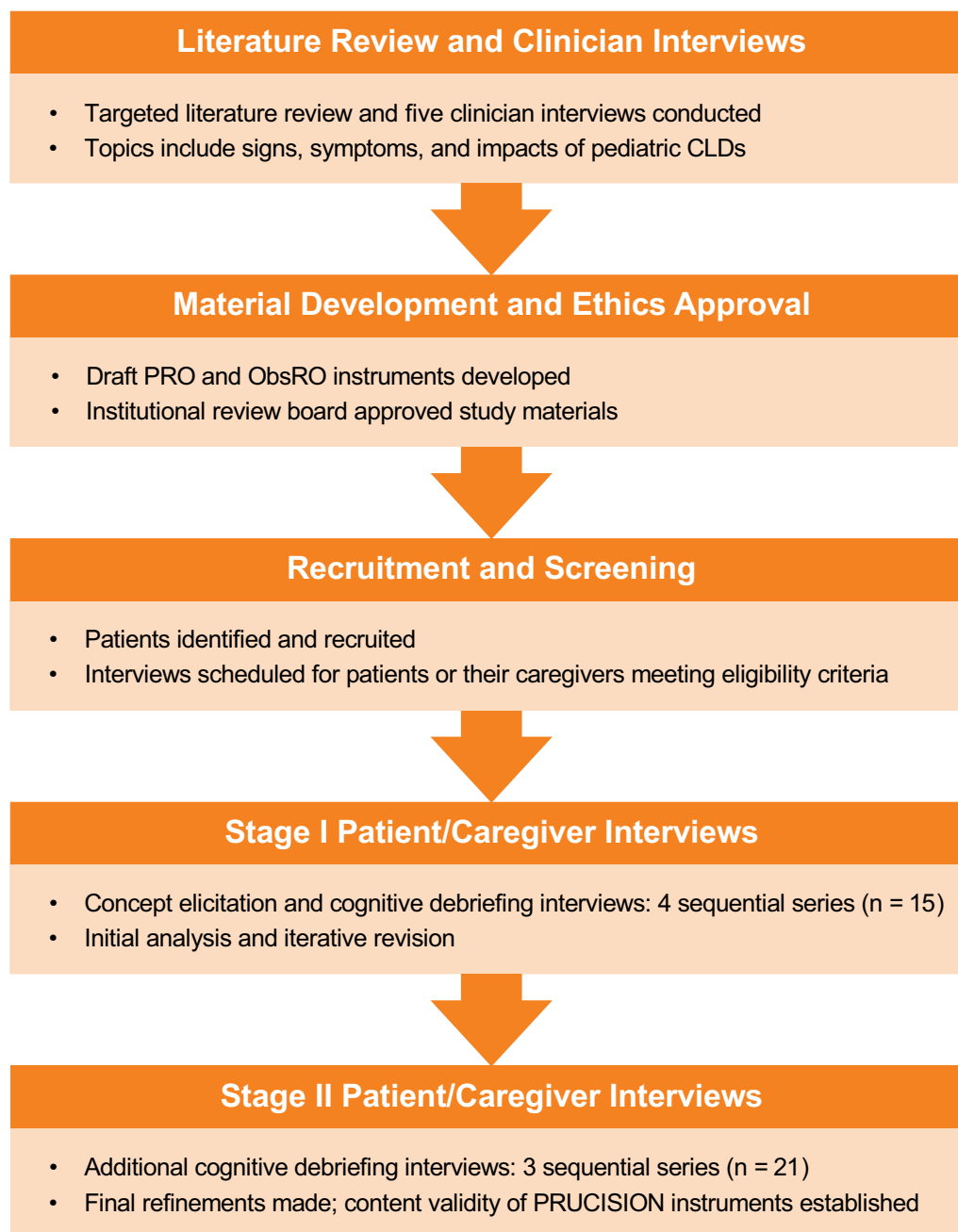


Fig. 1 Study flowchart. *CLD* cholestatic liver disease, *ObsRO* observer-reported outcome, *PRO* patient-reported outcome

they did not provide any detail on signs or symptoms of pruritus or CLDs, emphasized elderly patients with liver diseases, or focused on pruritus among pregnant patients. Finally, a search was conducted to identify clinical outcome assessment (COA) instruments that were in use at the time to assess the patient

experience of PFIC and other CLDs. After completion of the structured literature searches, additional ad hoc literature searches (e.g., reviewing reference lists of articles identified in structured searches) were performed. The reviews of the literature provided background

information that was used to plan for the interviews.

Clinician Interviews

Interviews with five expert clinicians were conducted to confirm and add to the initial literature review findings. These clinicians were based in major academic medical centers or centers that specialized in liver disease and/or sleep disorders across the United States. Interviews with three clinicians with PFIC expertise focused on the most relevant signs, symptoms, and impacts of pediatric CLDs, including PFIC. These clinicians were also asked about their perceptions of existing PRO instruments used to assess pruritus in PFIC and other CLDs and these instruments' relevance to the pediatric population. Interviews with two additional clinicians focused on sleep disturbance. Following completion of the literature review and clinician interviews, draft PRO and ObsRO instruments were developed.

Patient/Caregiver Interviews

Overview

Interviews with patients and/or their caregivers were conducted in two stages. In the first stage (i.e., stage I), interviews included both concept elicitation and cognitive debriefing steps. Concept elicitation interviews with patients and/or their caregivers were conducted to confirm the initial findings from the literature review and identify additional relevant features of CLD. Cognitive debriefing interviews were also conducted. Following initial feedback from stage I interviews, the draft PRO and ObsRO instruments were adjusted. Stage II interviews were primarily conducted to assess the appropriateness of the revised measures.

Recruitment and Inclusion Criteria

Patients and caregivers were recruited via a recruiting service (HealthUnlocked), social media sites, and physician referrals. Eligible patients were aged ≤ 18 years; resided in the United States, Canada, the United Kingdom, or Australia; had a diagnosis of PFIC, Alagille

syndrome, biliary atresia, or primary sclerosing cholangitis; and were diagnosed with cholestatic pruritus. Patients with previous liver transplantation were excluded.

Format

The format of these interviews varied depending on patient age (Table 1). For patients aged 1 to 5 years, telephone interviews were conducted with the caregiver, as patients younger than 6 years were assumed to be unable to reliably report on their condition. For patients aged 6–12 years, in-person interviews were conducted with both the patient and caregiver, and for patients aged 13–17 years, telephone interviews were conducted with both the patient and caregiver. During the interviews, participants were shown the PRO or ObsRO instruments on PowerPoint® slides. All interviews were audio recorded, and the audio files were deidentified and transcribed for subsequent data analysis.

Stage I Interviews

In these interviews, patients and caregivers were asked open-ended, probing questions about how they would describe the patient's symptoms, the impacts of these symptoms on functioning, and the frequency, severity, and duration of symptoms and impacts. Specifically, participants were asked to describe the following: their experience with cholestatic pruritus and other symptoms of CLDs; their first experience with the condition and how this may have changed over time; and current signs, symptoms, and impacts of the condition and its treatments. Participants were also asked to rate the disturbance associated with each reported symptom and daily impact on a 0–10 scale, with higher scores indicating greater disturbance. In cognitive debriefing interviews, patients and caregivers were asked to give feedback on the relevance and clarity of the PRO and ObsRO items and the instruments' instructions.

Initial Analysis and Revision

Concept elicitation interviews were evaluated for saturation, the point at which no new concepts were identified from the data. Additionally, concepts mentioned during these

Table 1 Summary of interviews (stages I and II)

Age group	Interview content	Interviewees	Interview format (duration, minutes)
Stage I			
Patients aged 1–5 years	Concept elicitation	Caregiver only	Telephone (60)
Patients aged 6–12 years	Cognitive debriefing of original instrument	Patient and caregiver	In-person (90)
Patients aged 13–17 years		Patient and caregiver (cognitive debriefing only)	Telephone (60)
Stage II			
Patients aged 1–5 years	Cognitive debriefing of instructions and revised instruments	Caregiver only	Telephone (60)
Patients aged 6–12 years	Card-sorting and meaningful-change tasks	Patient and caregiver	In-person (90)
Patients aged 13–17 years		Patient and caregiver	Telephone (90)

interviews were manually tagged with codes; the number of occurrences of each code (i.e., distinct concepts) was then summarized using Atlas.ti software (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). The average disturbance rating for each concept was calculated among all interviewees, as well as among a subgroup of patients with PFIC. Cognitive debriefing data were also reviewed to identify areas where changes could lead to improved understanding. Based on the stage I interviews, the research team modified, added, or removed concepts from the instruments, as appropriate.

Stage II Interviews

Stage II interviews aimed to evaluate patients’ and caregivers’ understanding of the revised instruments, determine what patients and caregivers considered a clinically meaningful change in pruritus, and define an appropriate age at which pediatric patients can begin to self-report. Specifically, stage II interviews consisted of several components: (i) cognitive debriefing after review of a new training guide that was developed to explain how to use the PRO and ObsRO instruments; (ii) cognitive debriefing after review of the revised PRO and ObsRO instruments; (iii) card-sorting exercises to assess patients’ understanding of a pictorial response scale; and (iv) a qualitative evaluation of meaningful change.

For the card-sorting exercise, patients aged 6 years and up were shown individual pictorial response options on separate cards. They were asked to sort them in order of severity or to compare two cards and indicate the one that was “feeling worse.”

In the qualitative meaningful-change task, patients and caregivers were asked how much a patient’s pruritus would have to decrease for them to consider the change meaningful. To assess this, patients (or caregivers) were asked to respond to three scenarios: (i) rate how bad their itching (or their child’s scratching) would have to be to prevent them from falling asleep and the level of itching where they could fall asleep; (ii) rate how bad their itching would have to be to stop them from playing or hanging out with their friends and the level of

itching where they could still play with their friends; and (iii) rate how bad their itching would have to be to bother them, but not stop them from doing the activities that they wanted to do and the level of itching that would not bother them. Estimates of meaningful change were obtained by subtracting the “unimpaired” rating (e.g., able to sleep) from the “impaired” rating (e.g., when itching was too intense to sleep).

Final Refinements

Patient and caregiver understanding of the instructions, concepts, and response scales was evaluated during stage II interviews, and final adjustments were made to the PRO and ObsRO instruments and associated training materials when gaps in understanding were observed. Ratings of meaningful change were summarized descriptively.

RESULTS

Clinician Interviews

In general, clinicians confirmed the findings from the literature review in terms of the signs, symptoms, and immediate impacts of cholestatic pruritus. For example, clinicians consistently emphasized the importance of pruritus and noted that it is most troublesome when a child goes to bed, can be exacerbated by warm weather, and that itching of the ears can be particularly troublesome. Clinicians also suggested that cholestatic pruritus varies in severity and age of onset depending upon the underlying CLD. They indicated that cholestatic pruritus is a more severe symptom and emerges earlier in life in PFIC and Alagille syndrome than in other CLDs such as biliary atresia or primary sclerosing cholangitis.

Suggestions from clinicians included the addition of “bone loss/brittle bones” to the initial listing of signs from the literature review. Clinicians emphasized that interference with sleep and difficulty focusing while in school are two key impacts of CLD and indicated that “impaired cognitive development” is too broad to be measured through this type of instrument.

In place of this concept, they suggested assessing difficulty focusing while in school and forming social bonds. They also noted that general impacts, such as depression or fatigue, are not easily attributable to cholestatic pruritus alone and may not be useful in instrument development. All clinicians agreed that existing instruments for assessing pruritus at the time that the interviews were conducted did not adequately measure the features and impacts of pediatric cholestatic pruritus. Examples of available instruments (and the patient populations in which they were initially described) that were reviewed with clinicians included the Pruritus Grading System (in patients with dermatologic or uremic conditions) [24], the Patient Benefit Index (in patients with pruritus of various origins) [25], the Eppendorf Itch Questionnaire (in patients with eczema) [26], the ItchyQoL (in adults with dermatologic conditions) [27], the 5-D itch scale (in adults with liver disease, kidney disease, dermatologic conditions, human immunodeficiency virus, or burn injuries) [28], the Children’s Dermatology Life Quality Index (in children with dermatologic conditions) [29], the Itch Severity Scale (in patients with psoriasis) [30], the Visual Analogue, Numerical Rating, and Verbal Rating Scales (in patients with chronic pruritus of any origin) [31], and the McGill Pain Questionnaire adapted for use in uremic pruritus [32]. In addition, examples of pruritus rating scales used in natural history or interventional studies in children with CLDs were also presented (e.g., as described in Kronsten et al. [33] and Hasegawa et al. 2014 [34], which used the scale described by Whittington [35] that is sometimes referred to as the Clinician Scratch Scale, or CSS [36]).

Based on the information gathered during the literature review and clinician interviews, initial versions of the PRO and ObsRO instruments for pediatric CLD (i.e., PRUCISION instruments) were drafted. These measures were to be completed twice daily (upon waking each morning and before going to bed) and covered concepts such as pruritus, pain, gastrointestinal problems, and sleep disturbance.

Patient and Caregiver Interviews

Study Participants

A total of 36 interviews were conducted with 28 patients and caregivers across the two stages; eight patients and caregivers were interviewed in both stages I and II. While the study was designed to include 21 patients and/or their caregivers in stage I interviews, only 15 were recruited, met eligibility criteria, and participated in stage I interviews, which were completed in four sequential series ($n = 5$, $n = 5$, $n = 4$, and $n = 1$, respectively), with modifications to the instruments made after each series. Twenty-one patients and/or their caregivers met eligibility criteria and were interviewed in stage II in three series ($n = 15$, $n = 1$, and $n = 5$, respectively). Series in stage I and II interviews that only included one interview each were due to receipt of regulatory feedback and subsequent revision of the instruments. A summary of patient characteristics among interviewees, including CLD type and age group, is shown in Table 2.

Stage I Interview Findings

Saturation, Symptoms, and Impacts During the stage I concept elicitation interviews, saturation was attained after eight interviews had been conducted. Patients and their caregivers indicated that pruritus was the most frequent and highly disturbing symptom associated with CLDs, with an average disturbance rating of 7.7 (Fig. 2a). In the subgroup of patients with PFIC, the average disturbance rating associated with pruritus was similar but slightly higher than in patients with non-PFIC diagnoses (Fig. 2b).

Overall, the impact that pruritus had on sleep was considered to be highly disruptive because it often interfered with the sleep of not only the patient but also the family. Sleep disturbance and fatigue were the most common impacts experienced by patients with CLDs and pruritus, with an average disturbance rating of 8.3 and 7.8, respectively (Fig. 3a). In the subgroup of patients with PFIC, the average disturbance ratings associated with sleep disturbance and fatigue were similar but slightly higher than in patients with non-PFIC

Table 2 Summary of patient characteristics among interviewees

Diagnosis	Age category, <i>n</i>			Total
	1–5 years	6–12 years	13–17 years	
PFIC	7	9	1	17
Alagille syndrome	5	4	2	11
Biliary atresia	0	3	0	3
Primary sclerosing cholangitis	0	1	4	5
Total	12	17	7	36 ^a

PFIC progressive familial intrahepatic cholestasis

^aEight patients participated in two separate series of interviews for a total of 28 unique patients interviewed and 36 total patient/caregiver interview sessions

diagnoses (Fig. 3b). Many caregivers reported that their children were highly irritable as a result of fatigue and constant pruritus. Several quotes from caregivers of patients with CLDs, presented in Table 3, illustrate patients' experience with pruritus, which seems to be particularly bothersome at night.

The frequency and average disturbance ratings of other commonly reported symptoms and impacts in all patients and in patients with PFIC or other diagnoses are depicted in Figs. 2 and 3.

Insights from Stage I Cognitive Debriefing Interviews and Summary of Changes Made

After the stage I cognitive interviews, several refinements were made to the PRO and ObsRO instruments based on feedback from patients and caregivers. First, wording adjustments were made to certain phrases so they would be easier for children to understand. For example, several children questioned the meaning of the word "moderate," so it was replaced with the word "medium." In addition, the original instruction of "please rate" the itching was simplified to "how bad is" the itching. Wording changes in the PRO were carried over to the ObsRO for consistency. Second, several concepts were either removed or expanded based on the

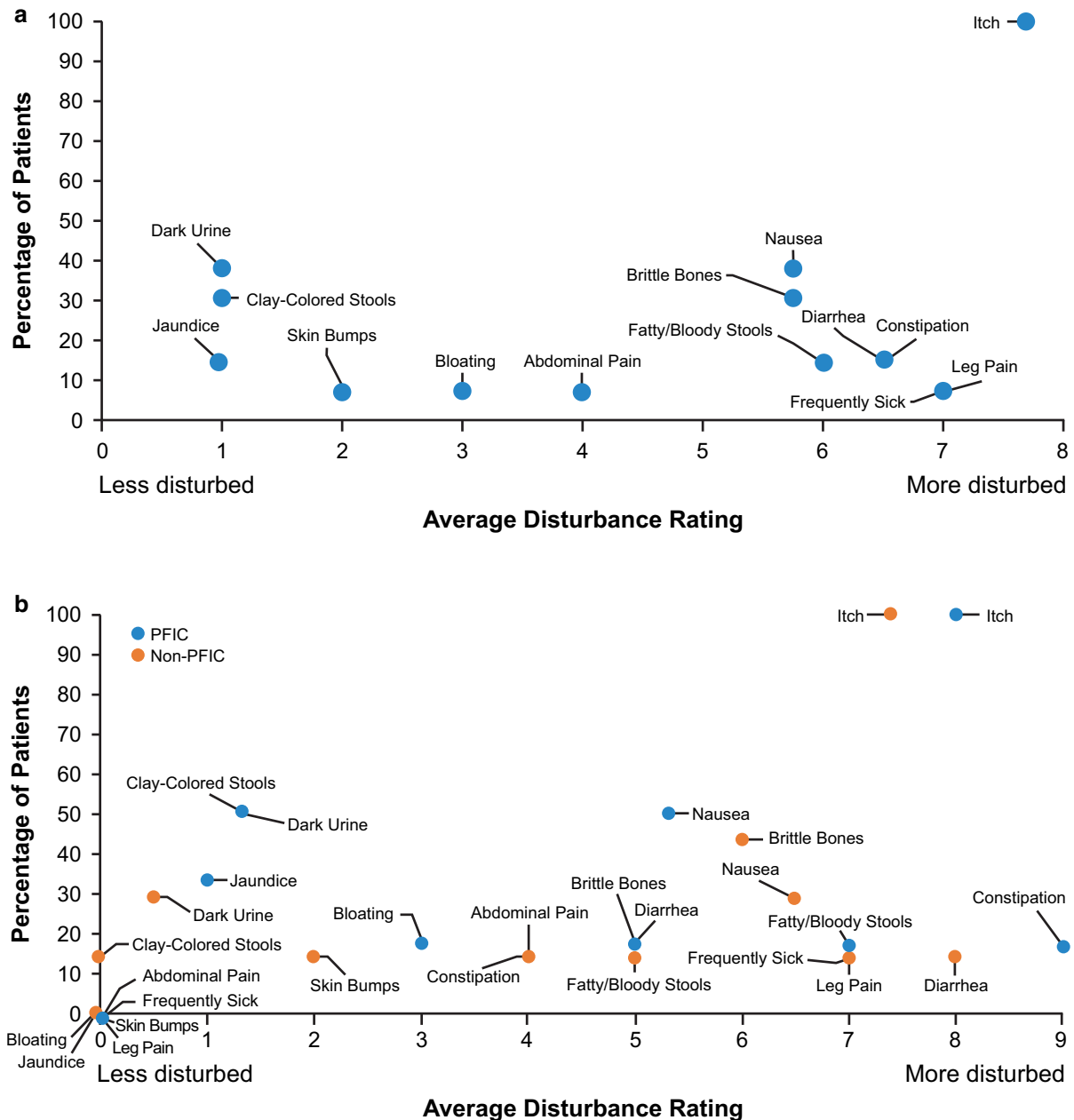


Fig. 2 Patient/caregiver-reported symptoms and associated disturbance in pediatric cholestatic liver diseases in all patients (**a**) and by subgroups of patients with PFIC or other diagnoses (i.e., non-PFIC) (**b**). Based on sample of

$n = 13$; disturbance ratings were not obtained during two patient interviews. *PFIC* progressive familial intrahepatic cholestasis

information gathered during the interviews. For example, concepts that were identified in the literature review or included following clinician interviews were not considered as relevant to patients and caregivers (e.g., gastrointestinal

symptoms, pain) and were subsequently removed from the PRO and ObsRO instruments. Furthermore, caregivers considered sleeping with and soothing their children to be two separate concepts, so these were split into

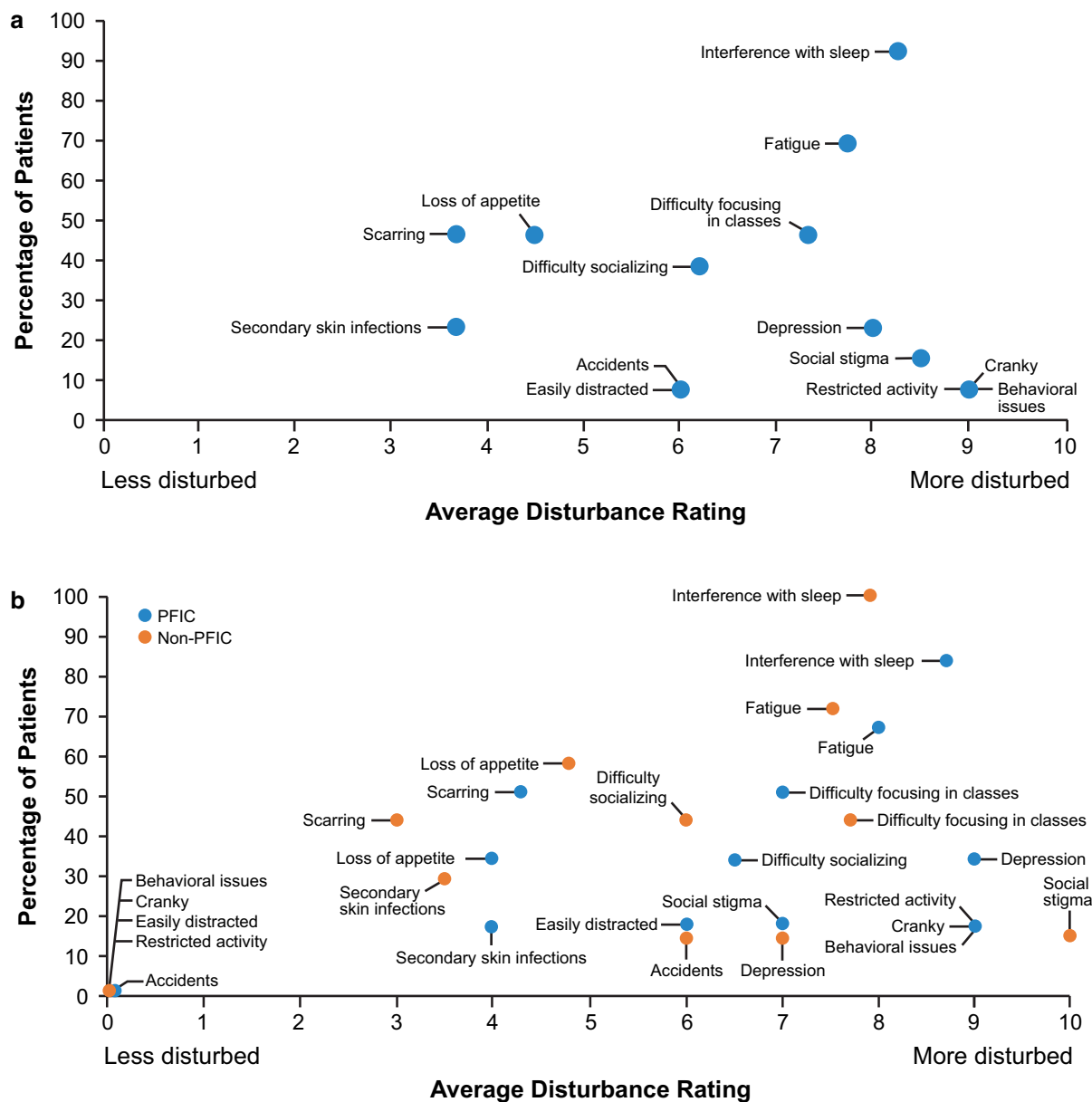


Fig. 3 Patient/caregiver-reported impacts and associated disturbance in pediatrics with cholestatic liver diseases and pruritus in all patients (a) and by subgroups of patients with PFIC or other diagnoses (i.e., non-PFIC) (b). Based

on sample of $n = 13$; disturbance ratings were not obtained during two patient interviews, and ratings for fatigue were only reported by eight interviewees. *PFIC* progressive familial intrahepatic cholestasis

separate items when the instruments were revised. Finally, the PRO and ObsRO instruments were modified to use a five-point pictorial faces scale instead of a verbal response scale, and a training guide for caregivers was created.

Stage II Interview Findings

The major adjustments made following the stage II interviews were the addition of details to the caregiver training guide and modifications to the ObsRO instrument instructions. Specifically, in the caregiver training, a few

Table 3 Select quotations from caregivers of patients with cholestatic liver disease on the patient experience of pruritus and associated impacts

Respondent and patient details	Caregiver perspective
Parent of male patient, age 1 year, with Alagille syndrome	"...[He] does need a caregiver to help him go to sleep. He'll itch until you can get him settled and actually asleep for the night"
Parent of male patient, age 1 year, with Alagille syndrome	"At night, he will kick his legs. He doesn't necessarily rub them together, but he will kick them when they really itch. If he's having a really bad night, he's kicking a lot. He's very restless. He cries a lot like he's in pain. He'll be in pain and crying but he doesn't want you to touch him. He's pretty inconsolable"
Parent of female patient, age 2 years, with Alagille syndrome	"...[We've] noticed that my daughter gets aggressive when she's itchy. It's her way—since she doesn't speak a lot—of expressing herself, so she becomes very aggressive when she's itchy"
Parent of female patient, age 2 years, with Alagille syndrome	"She'll scratch from like midnight until 4:00 in the morning"
Parent of female patient, age 12 years, with biliary atresia	"The warmer it gets outside, the warmer she is, she starts to scratch more"
Parent of male patient, age 7 years, with PFIC	"He'll come to me and say can you scratch if it's a spot he can't get to"

PFIC progressive familial intrahepatic cholestasis

sentences were added to give caregivers examples of what could be considered scratching behavior. For example, observable pruritus-related behaviors in patients could include scratching with their hands, scratching by rubbing their body parts against objects, asking their parents to scratch them, restlessness, kicking of legs, and/or crying/irritability and complaints about itching. The instructions in the ObsRO were then revised to align with the caregiver training material, such that caregivers were asked to think about all of the different types of scratching behaviors when rating their child's scratching.

Card-Sorting Task A total of 13 patients completed the card-sorting task. All of these patients could correctly sort the cards in order from "feeling ok" to "feeling the worst," and when comparing two cards, all patients correctly identified which card was "feeling worse." Therefore, it was determined that children aged ≥ 6 years could differentiate between all

five faces of the pictorial scale and understood their order, supporting the content validity of this rating scale.




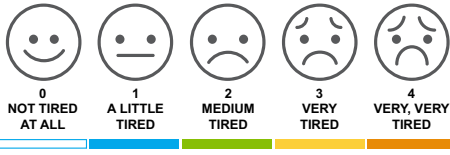
Qualitative Assessment of Meaningful Change Potential thresholds for meaningful within-patient change were explored in 19 stage II interviews. Interviewed patients and caregivers indicated that an approximately two-point decrease in itching or scratching on the five-point pictorial scale would constitute a meaningful change. However, this estimate should be considered preliminary, as patients did not experience actual changes in pruritus during the course of instrument development.

Quantitative measurement characteristics, including an empirically derived threshold for clinically meaningful change in pruritus score, were established based on an independent, blinded, psychometric analysis that is the subject of a companion article in this issue. In brief, the psychometric performance of the ObsRO PRUCISION instrument was evaluated using

a

PRO Morning Diary (to be completed shortly after waking each morning)

Please answer the questions on the following screens. There are no right or wrong answers.
Please think about the time since you went to bed last night (beginning when you started trying to fall asleep).

<p>1. How bad was your worst itching since you went to bed last night?</p>	 <p>0 NO ITCHING 1 A LITTLE ITCHING 2 MEDIUM ITCHING 3 A LOT OF ITCHING 4 THE WORST ITCHING</p>
<p>2. How hard was it to <u>fall</u> asleep last night because of your itching?</p>	 <p>0 NOT HARD AT ALL 1 A LITTLE HARD 2 MEDIUM HARD 3 VERY HARD 4 VERY, VERY HARD</p>
<p>3. How hard was it to <u>stay</u> asleep last night because of your itching?</p>	 <p>0 NOT HARD AT ALL 1 A LITTLE HARD 2 MEDIUM HARD 3 VERY HARD 4 VERY, VERY HARD</p>
<p>4. Did you wake up last night because of itching?</p>	<p>No Yes</p>
<p>5. How tired do you feel this morning?</p>	 <p>0 NOT TIRED AT ALL 1 A LITTLE TIRED 2 MEDIUM TIRED 3 VERY TIRED 4 VERY, VERY TIRED</p>

PRO Bedtime Diary (to be completed when going to bed each night)

Please answer the questions on the following screens. There are no right or wrong answers.
Please think about the time since you woke up this morning.

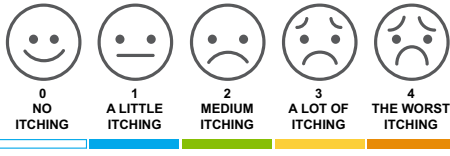

<p>1. How bad was your worst itching since you woke up this morning?</p>	 <p>0 NO ITCHING 1 A LITTLE ITCHING 2 MEDIUM ITCHING 3 A LOT OF ITCHING 4 THE WORST ITCHING</p>
<p>2. How tired were you since you woke up this morning?</p>	 <p>0 NOT TIRED AT ALL 1 A LITTLE TIRED 2 MEDIUM TIRED 3 VERY TIRED 4 VERY, VERY TIRED</p>

Fig. 4 Final PRUCISION PRO (a) and ObsRO (b) instruments to assess pruritus and sleep characteristics in patients with pediatric cholestatic liver diseases. *ObsRO* observer-reported outcome, *PRO* patient-reported outcome

b

ObsRO Morning Diary (to be completed shortly after child wakes up each morning)

Please answer the questions on the following screens. There are no right or wrong answers. Please think about the time since your child went to bed last night (beginning when your child started trying to fall asleep). As a reminder, when we use the term “scratching,” we would like you to think about all of the different types of scratching behaviors that you can see.

1. How bad was your child’s worst scratching since he/she went to bed last night?	0 NO SCRATCHING 1 A LITTLE SCRATCHING 2 MEDIUM SCRATCHING 3 A LOT OF SCRATCHING 4 WORST POSSIBLE SCRATCHING
2. Since your child went to bed last night, did you see blood due to scratching?	No Yes
3. Did your child need a caregiver to help him/her fall asleep last night due to his/her itching?	No Yes
4. Did your child need a caregiver to soothe him/her at some point during the night last night due to his/her itching?	No Yes
5. Did your child need a caregiver to sleep with him/her at some point during the night last night due to his/her itching?	No Yes
6. How many times did you notice that your child woke up last night?	Enter a number from 0 to 99

ObsRO Bedtime Diary (to be completed when child is going to bed each night)

Please answer the questions on the following screens. There are no right or wrong answers. Please think about the time since your child woke up this morning. As a reminder, when we use the term “scratching,” we would like you to think about all of the different types of scratching behaviors that you can see.

1. How bad was your child’s worst scratching since he/she woke up this morning?	0 NO SCRATCHING 1 A LITTLE SCRATCHING 2 MEDIUM SCRATCHING 3 A LOT OF SCRATCHING 4 WORST POSSIBLE SCRATCHING
2. How tired does your child seem to be today?	0 NOT TIRED AT ALL 1 A LITTLE TIRED 2 MEDIUM TIRED 3 VERY TIRED 4 VERY, VERY TIRED

Fig. 4 continued

data from the phase 3, randomized, placebo-controlled study of odevixibat in patients with PFIC (NCT03566238) [37]. Scores on the PRUCISION scale in this patient population were compared with scores from other established

rating scales (i.e., patient-, caregiver-, and clinician-reported Global Impression of Change and Global Impression of Symptoms scales; Pediatric Quality of Life Inventory and family impact module) to test the instrument’s

reliability, construct validity, and sensitivity to change.

Age at Administration Over the course of the stage II interviews, the minimum age at which the PRO instrument could be administered was determined based on multiple factors, including a patient's ability to pay attention over the course of the interview, read the items, answer the items, explain what the items meant to them, complete the card-sorting task, or answer the meaningful-change questions. In general, patients aged 6 to 8 years had difficulty responding to the PRO items appropriately, even with support from their caregiver. Therefore, it was decided that the ObsRO instrument was to be used for patients younger than 8 years of age, while the PRO instrument could be used in patients aged 8 years and older.

Final Developed Instruments

The PRO and ObsRO instruments were finalized following completion of the stage II interviews. The final developed PRUCISION instruments are depicted in Fig. 4a and b, respectively. For each PRUCISION instrument, intended to be administered once in the morning and once in the evening in an electronic diary format, it takes users approximately 1–2 minutes to complete each assessment.

DISCUSSION

In this qualitative study, novel PRO and ObsRO instruments, called PRUCISION, were created as COAs to characterize the patient experience of cholestatic pruritus in children. During the development process, evidence was gathered from multiple sources, including the literature and interviews with expert clinicians, patients, and caregivers. The final developed instruments cover concepts that were identified as the most meaningful to pediatric patients with CLD and their caregivers, namely pruritus and sleep disturbance.

In a recent systematic review of PROs used in studies of primary biliary cholangitis and primary sclerosing cholangitis conducted from

1990 to 2019, only 4 of 318 identified publications (1%) measured any PRO concepts in pediatric patients [38]. Further, only two of these used a PRO instrument, and these were different from each other. In the current study, interviewed clinicians indicated that COAs existing at the time the interviews were conducted did not adequately measure the features and impacts of pediatric cholestatic pruritus. Altogether, this indicated a need for standardized instruments to address pruritus in a manner that was relevant to pediatric patients with CLD [39].

At the time this study commenced, existing COAs to measure pruritus in clinical settings [40] had been developed primarily for specific dermatologic conditions (e.g., the Patient-Oriented SCORing Atopic Dermatitis [PO-SCORAD] [41]) or were primarily characterized in adult populations (e.g., the 5-D itch scale [28] and Visual Analog, Numerical Rating, and Verbal Rating Scales [31]). While these measures have been adapted for clinical use in pediatric patients with CLD [42, 43], few scales have been specifically developed and validated in this patient population [11]. Limitations of existing scales designed for use in pediatric patients with CLD include lack of validation [33, 44] or generation of clinician-reported scores only and/or assessment of pruritus without considering the burden on the patient more generally (i.e., the Whittington-itch scale/CSS) [35, 45]. The PRUCISION instruments developed here were designed for pediatric patients with CLD to characterize pruritus and sleep disturbance from caregiver and patient perspectives using easy-to-understand questions and responses; these instruments were also validated, the results for which are presented in the companion article.

While this study was underway, another set of instruments for assessing the impact of itching in pediatric cholestasis was developed with PRO and ObsRO components: the Itch Reported Outcome (ItchRO) Patient (or ItchRO [Pt]) and ItchRO Observer (ItchRO [Obs]), respectively [46]. These were developed primarily in a population of children with Alagille syndrome, but they have been subsequently employed in patients with PFIC [47]. In the current study, four types of patients with pediatric CLD were

included, and patients with PFIC or their caregivers (47%) were the most common interviewees. Other similarities exist between the ItchRO and the PRUCISION instruments, such as both having morning and bedtime pruritus assessments, measures of sleep disturbance, five-point response scales, and administration via electronic diaries. However, PRUCISION differs from ItchRO in several ways, including more questions focused on sleep disturbance (5–6 in PRUCISION v.s. 2 in the ItchRO) [46], use of pictorial face response options in PRUCISION to help younger patients express the severity of their symptoms, and age at administration (PRUCISION PRO can be administered to patients ≥ 8 years old while the ItchRO (Pt) can be administered to patients ≥ 9 years old [46]). Given the paucity of tools previously available, gaining a better understanding of how children and their caregivers experience CLDs through instruments such as these may facilitate the development and testing of new treatments for these diseases.

The PRUCISION PRO and ObsRO instruments developed here followed industry and regulatory best practice guidelines [18–21]. According to these guidelines, PRO measures should aim to provide the patient perspective on treatment benefits; these can be supplemented with reports of observable disease-related behaviors by caregivers for patients who cannot report for themselves (i.e., very young children) [18]. In developing PRO measures, it is also important to determine the lower age limit at which children can understand the questions and provide reliable and valid responses. Here, it was found that patients aged ≥ 8 years could reliably use the PRO, whereas for patients aged < 8 years, the ObsRO should be used, which is consistent with recommendations for PRO measures [48]. The development of both PRO and ObsRO PRUCISION instruments may allow for a broader scope of pruritus information to be collected in clinical trials (i.e., data can be captured for patients with a range of ages).

The small sample size of interviewees, particularly those with biliary atresia, could be considered a study limitation. This primarily results from the diseases assessed in this study

being rare disorders in children [1–3]. To ensure that all relevant signs, symptoms, and impacts were identified, caregivers were also invited to participate in the interviews that informed instrument development. A strength of this study was the inclusion of patients with multiple pediatric CLDs, which allowed the most salient shared symptoms and impacts to be identified.

In conclusion, a systematic approach was undertaken to develop the PRUCISION PRO and ObsRO instruments, including extensive input from patients and caregivers to confirm the content validity of those instruments. The final instruments focus on a prominent and problematic symptom and its impact (pruritus and sleep disturbance, respectively) identified by pediatric patients with CLD and their caregivers.

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Karlsson is a current employee of Albireo. Natalie Warholc, Lise Kjems, and Patrick Horn were employees of Albireo at the time of the study. Natalie Warholc is currently an employee of Ribon Therapeutics. Lise Kjems is currently an employee of Cyclo Therapeutics. Patrick Horn is currently an employee of HemoShear Therapeutics.

Compliance with Ethics Guidelines. The study protocol, informed consent language, recruitment material, and other supporting information were submitted to an independent institutional review board (New England Institutional Review Board, Newton, MA, USA) for approval prior to study initiation. In addition, this study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. All study participants provided informed consent before any interviews were performed or any data were collected.

Data Availability. Qualified academic investigators and researchers may request additional de-identified data and supporting documents pertaining to this study. For details regarding data availability, instructions for requesting information, and our data disclosure policy, please email medinfo@albireopharma.com.

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