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Content evaluation of pruritus, skin pain and sleep disturbance patient-reported outcome measures for adolescents and adults with moderate-to-severe atopic dermatitis: qualitative interviews

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Abstract

Background Pruritus, skin pain and sleep disturbance place a significant burden on individuals with moderate-to-severe atopic dermatitis (AD) and negatively affect their quality of life. Fit-for-purpose patient-reported outcome measures (PROMs) that assess AD-related pruritus, skin pain and sleep disturbance are important for evaluating the effectiveness of new AD treatments.

Objectives To evaluate the content validity of five AD-related PROMs in adolescents and adults with moderate-to-severe AD [the Worst Pruritus Numeric Rating Scale (NRS), the AD Skin Pain NRS, the Sleep Disturbance NRS, the skin pain-specific Patient Global Impression of Change (PGIC) and the skin pain-specific Patient Global Impression of Severity (PGIS)], and to assess patient-reported experience with pruritus, skin pain and sleep disturbance.

Methods A qualitative study in adolescents (aged 12–17 years) and adults (aged ≥ 18 years) with moderate-to-severe AD was conducted in two consecutive stages. In each stage, two iterative rounds of individual interviews were conducted by experienced interviewers. All interviews included concept elicitation and cognitive debriefing components. Data were analysed using thematic analysis.

Results Twenty-seven adults and 20 adolescents with moderate-to-severe AD took part in the initial content evaluation (stage 1) of the Worst Pruritus NRS (1.0) and AD Skin Pain NRS (1.0) ($n = 26$; 16 adults, 10 adolescents) and in the subsequent content evaluation (stage 2) of the revised Worst Pruritus NRS (1.1), revised AD Skin Pain NRS (1.1), Sleep Disturbance NRS, skin pain-specific PGIC and skin pain-specific PGIS ($n = 21$; 11 adults, 10 adolescents). The results were generally aligned and consistent for adult and adolescent participants. Additionally, we found that sleep disturbance is relevant and important for evaluation in adults and adolescents with moderate-to-severe AD (stage 2), while also providing further confirmation of this for pruritus and skin pain (stages 1 and 2).

Conclusions Our findings support the content validity of the revised Worst Pruritus NRS (1.1), revised AD Skin Pain NRS (1.1), Sleep Disturbance NRS, skin pain-specific PGIC and skin pain-specific PGIS in individuals aged ≥ 12 years with moderate-to-severe AD. Furthermore, the findings support sleep disturbance, skin pain and pruritus as being relevant and important for adolescents and adults with moderate-to-severe AD.

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Lay summary

Atopic dermatitis (or 'AD' for short) is also known as 'eczema'. It causes itchy, dry and painful or inflamed skin. AD affects millions of people in the USA and many cases are moderate or severe. As treatments for AD are developed, clinical trials need ways to measure how well a treatment works. Patient-reported outcome measures (or 'PROMs') are questionnaires answered only by patients that record people's experiences with their condition or treatment.

We interviewed 27 adults and 20 adolescents with moderate-to-severe AD to see how well five different PROMs measuring AD symptoms line up with real experiences. Based on their answers, we found that adults and adolescents have similar experiences with AD symptoms, including itch, skin, pain and sleep disturbance.

Our results suggest that these PROMs are easy to understand when people with AD are asked about their most important symptoms. The interviews confirmed that itch, skin pain and sleep disturbances cause major problems and disruptions for people with AD. This highlights the need to track these symptoms and their effects in clinical trials for AD treatments.

What is already known about this topic?

- Pruritus, skin pain and sleep disturbance place a significant burden on individuals with moderate-to-severe atopic dermatitis (AD) and negatively impact their quality of life.
- Fit-for-purpose patient-reported outcome measures that assess pruritus, skin pain and sleep disturbance in patients with AD are important for evaluating the effectiveness of new treatments.

What does this study add?

- These findings support the content validity of the revised Worst Pruritus Numeric Rating Scale (NRS), the revised AD Skin Pain NRS, the Sleep Disturbance NRS, the skin pain-specific Patient Global Impression of Change and the skin pain-specific Patient Global Impression of Severity in individuals aged ≥ 12 years with moderate-to-severe AD.
- The findings support pruritus, skin pain and sleep disturbance as being relevant and important for adolescents and adults with moderate-to-severe AD.

What are the clinical implications of this work?

- For clinical practitioners and clinical trial researchers evaluating treatment benefit, this research further highlights the importance of assessing not only pruritus and skin pain, but also sleep disturbance, in adolescents and adults with moderate-to-severe AD.

Atopic dermatitis (AD) is a chronic skin disorder characterized by pruritus and inflammation.[1] This condition affects an estimated 7.3% of adults and 9.3% of adolescents (aged 12–17 years) living in the USA, with nearly 40.0% of adult cases and 55.0% of adolescent cases categorized as moderate or severe.[2,3] Common signs, symptoms and impacts of AD include pruritus, excessive dryness, skin pain, inflamed skin and sleep disturbance.[4] Pruritus, skin pain and sleep disturbance, in particular, place a significant burden on individuals with moderate-to-severe AD and negatively affect their quality of life.[5,6]

Capturing input from patients to determine what they consider to be meaningful aspects of health is an integral part of the medical product development process. Patient-reported outcome measures (PROMs) are standardized instruments developed to collect evidence of health or treatment outcomes directly from patients without interpretation by a clinician; PROMs are used to support the evaluation of a treatment or intervention.[7] It is crucial to assess attributes, such as content validity, to determine if a newly developed PROM is appropriate, accurate, reliable and valid for use in evaluating a treatment outcome (i.e. fit for purpose).[7–10]

Fit-for-purpose PROMs that assess AD-related pruritus, skin pain and sleep disturbance are important for the comprehensive evaluation of the effectiveness of new AD treatments alongside clinical measures, such as the Eczema Area and Severity Index (EASI), the Investigator Global Assessment (IGA), and calculations of the percentage of affected body surface area.[7,11–13] Although single-item PROMs assessing peak pruritus, skin pain and sleep disturbance in adolescents and adults with AD were recently published and/or included in product labels, the specific wording of these measures were not publicly available for inclusion in early clinical trials of new treatments in development for this same population.[6,14–16] Therefore, to support the continued evaluation of a new AD treatment and future product labelling,[17] new single-item PROMs assessing AD-related pruritus, skin pain and sleep disturbance were developed through multistage research collaborations between clinical and instrument development experts at a nonprofit research institute (RTI Health Solutions) and sponsor organizations (Kyowa Kirin and Amgen). These PROMs were developed in accordance with U.S. Food and Drug Administration (FDA) patient-reported outcomes and patient-focused drug development

guidance,[7,8] as well as direct FDA feedback, prior to undergoing content validation to support the reliability and validity of these measures.[8–10]

Here, we present our findings from the two-stage evaluation of content validity of five PROMs assessing pruritus, skin pain and sleep disturbance in adolescents and adults with moderate-to-severe AD, including qualitative findings on the patient-reported experience with these AD-related symptoms.

Materials and methods

This qualitative study in adolescents and adults with moderate-to-severe AD [Patient-Oriented Eczema Measure (POEM) score of ≥ 8] was conducted in two consecutive stages [Figure 1; Table S1 (see Supporting Information)]. In stage 1, we tested the content validity of two initial single-item PROMs: the Worst Pruritus Numeric Rating Scale (NRS; version 1.0, initially developed by in-house clinical experts at Kyowa Kirin) and two versions of the AD Skin Pain NRS (i.e. version 1.0, initially developed through collaboration between Kyowa Kirin and RTI Health Solutions), developed to assess worst itch and skin pain, respectively, in adolescents and adults with moderate-to-severe AD. Of note, the Worst Pruritus NRS was referred to as the 'Pruritus NRS' in a previous publication.[18] We additionally explored the patient experience with AD-related symptoms, with a primary focus on pruritus and skin pain.

Through collaborations between clinical and instrument development experts at Kyowa Kirin, Amgen and RTI Health Solutions, the Worst Pruritus NRS (1.0) and the AD Skin Pain NRS (1.0) were revised in response to feedback received from participants during stage 1,

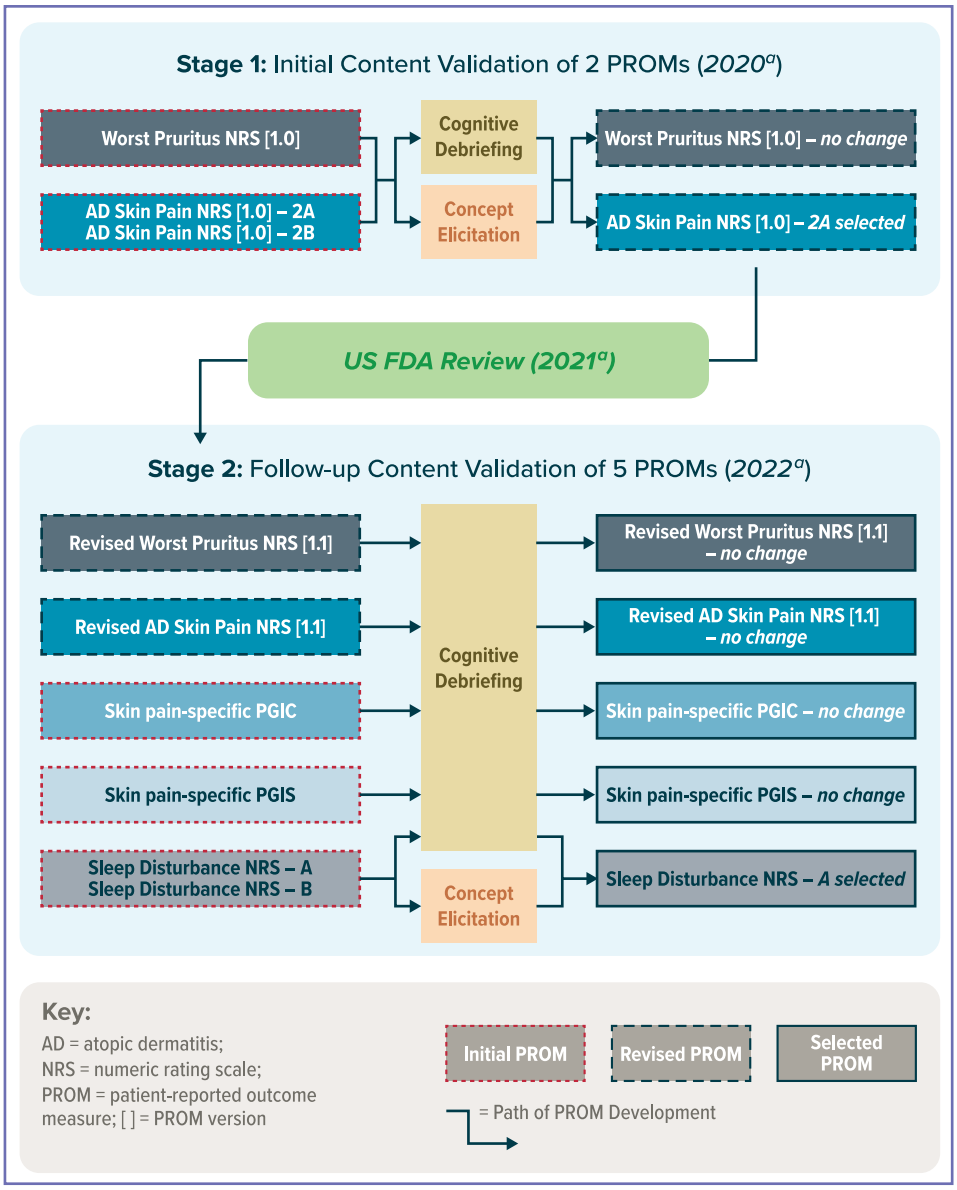

Figure 1 Development and content validation process for the five atopic dermatitis (AD) patient-reported outcome measures (PROMs). US FDA, U.S. Food and Drug Administration; NRS, numeric rating scale; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity. [a]Year represents the start of each stage or review period.

as well as feedback received from the FDA between stages 1 and 2, in order to develop the revised Worst Pruritus NRS (i.e. version 1.1) and the revised AD Skin Pain NRS (i.e. version 1.1).Subsequently in stage 2, we assessed the content validity of five total PROMs: the two revised PROMs from stage 1 (i.e. revised Worst Pruritus NRS 1.1 and revised AD Skin Pruritus NRS 1.1) and three new PROMs with the same target population, developed through collaborations between RTI Health Solutions, Kyowa Kirin and/or Amgen. These included (i) two versions of a single-item Sleep Disturbance NRS (A and B) to assess the impact of AD on sleep; (ii) the skin pain-specific Patient Global Impression of Change (PGIC); and (iii) the skin pain-specific Patient Global Impression of Severity (PGIS) (Table S1). We also explored the relevance and importance of assessing sleep disturbance to support evaluation of the Sleep Disturbance NRS.

All interviews included both concept elicitation and cognitive debriefing components, with the aim of evaluating the content validity for each of the final PROMs (Figure 1), and revising the PROMs if supported by participant feedback. Concept elicitation was performed to understand first-hand the relevance and importance of pruritus, skin pain and sleep disturbance to adolescents and adults with moderate-to-severe AD. Cognitive debriefing was performed to assess whether participants understood the PROM instructions, questions, response options and recall periods. The RTI International Institutional Review Board reviewed the study materials and provided expedited approval for each stage of the research prior to participant recruitment. A qualitative research firm (L&E Research; https://www.leresearch.com) was responsible for the recruitment, screening and scheduling of study participants. Using their database of individuals who had previously expressed interest in participating in qualitative research, L&E Research employed a purposive sampling approach to identify possible participants in the USA and screen for eligibility criteria (Table 1). For all interviews, informed consent (for adults) or caregiver permission and child assent (for adolescents) was obtained prior to participation.

In both stages, two iterative rounds of 45-min telephone- and online-based audio-recorded individual interviews were conducted by two experienced interviewers using a semi-structured discussion guide and then transcribed. There were no differences in the semi-structured discussion guide for adult or adolescent participants. PROMs and study questions were visually presented during the course of the interview via shared computer screen using Zoom (https://zoom.us). To avoid potential difficulties with participants being unable to view the onscreen questions, an electronic copy of the PROMs was provided in advance, with instructions not to review the questions until instructed to do so by the interviewer. One interviewer recorded field notes and ensured no content was missed, while the other led the interview. Immediately after each round of interviews, interviewers debriefed and recorded in Microsoft Excel their initial thoughts from the interviews pertaining to the items and other key issues (e.g. clarity and optimization of wording and response choices, ease of understanding and response), on the basis of field notes. Following the conclusion of the interviews, all audio files were transcribed verbatim, de-identified and prepared for analysis. Data from the interview transcripts were analysed using thematic analysis aided by field notes.[9,10] Descriptive statistics were summarized for all demographic and clinical data collected at screening.

Stage 1: Initial content evaluation of the Worst Pruritus Numeric Rating Scale (NRS) and atopic dermatitis Skin Pain NRS

Each interview began with brief concept elicitation, in which participants were asked a series of open-ended questions designed to obtain spontaneous reports of AD-related symptoms. Interviewers then asked participants to describe their AD-related itch and skin pain experience (if not raised spontaneously), how these symptoms affect their daily lives and the extent of bother on a scale from 0 (not at all bothersome) to 10 (extremely bothersome). Other AD symptoms were not uniformly asked about. Next, during cognitive debriefing, participants were asked to review and provide feedback on the initial Worst Pruritus NRS (1.0) item and two proposed AD Skin Pain NRS (1.0) items with slightly different wording (versions 2A and 2B; Table S1), presented in a different order each round using a 'think-aloud' process. Specifically, participants were asked about the clarity and interpretation of the instructions, items and response scales; appropriateness

Table 1 Eligibility criteria

Eligibility criteria for both studies
- Aged ≥ 12 years
- Had moderate-to-severe AD, based on their responses to the POEM (POEM score ≥ 8)
- Had not participated in an AD-related qualitative study or clinical trial in the previous 6 months
- Were fluent in English
- Resided in the USA
- Were willing and able to consent and participate in a 45-min telephone and online interview
- (Adolescents only) Had a caregiver (i.e. a parent or legal guardian) who was willing to provide verbal permission and participate in the first 5 min of the telephone and online interview to affirm parental permission to proceed with the interview

Unique eligibility criteria for the initial content evaluation of two PROMs (stage 1)
- Had a clinician diagnosis of AD for at least 1 year
- Had experienced at least moderate AD-related pruritus and skin pain in the previous 2 weeks

Unique eligibility criteria for the content evaluation of five PROMs (stage 2)
- Had a clinician diagnosis of AD for at least 6 months
- Had experienced AD-related pruritus, skin pain and sleep disturbance in the previous 2 weeks
- Had used a prescription cream, ointment or other prescription medicine for treatment of AD in the past 6 months

AD, atopic dermatitis; POEM, Patient Oriented Eczema Measure; PROM, patient-reported outcome measure.

of the recall period; and relevance and relative importance of the concepts/items to their experience with AD. Sample questions and probes from the interview guide for stage 1 are included in Table S2 (see Supporting Information).

Stage 2: Content evaluation of five atopic dermatitis patient-reported outcome measures

Following the initial content evaluation in stage 1, the Worst Pruritus NRS (1.0) and the AD Skin Pain NRS (1.0) were simplified in response to feedback received from the FDA before undergoing further cognitive debriefing in stage 2. In stage 2, each interview began with cognitive debriefing of the revised Worst Pruritus NRS (1.1) and revised AD Skin Pain NRS (1.1). Next, the two versions of the Sleep Disturbance NRS (A and B; Table S1) were cognitively debriefed. For an abbreviated concept elicitation, questions were asked to better understand the relevance and importance of assessing AD-related sleep disturbance. Participants were also asked about whether (and how) sleep disturbance is relevant to their experience with AD and whether it is important to assess. If not reported spontaneously, participants were probed further on trouble falling asleep, night-time wakening, early morning wakening, insufficient amount of sleep and feeling unrested upon awakening due to AD. Lastly, two newly developed skin-specific global items – the skin pain-specific PGIC and the skin pain-specific PGIS – were cognitively debriefed in response to feedback from the FDA for qualitative evaluation of these two items. The same 'think-aloud' approach described for stage 1 to debrief all items was also employed for stage 2. Additionally, using the item-response choices, participants were asked questions about the amount of change on the Sleep Disturbance NRS (versions A and B), as well as skin pain-specific PGIS and PGIC items that would be deemed meaningful from their perspective. Sample questions and probes from the interview guide for stage 2 are included in Table S2.

Measure descriptions

All PROMs included in these studies are summarized in Table S1. Two measures were assessed in stage 1: the single-item Worst Pruritus NRS (1.0) and two versions of the single-item AD Skin Pain NRS (versions 2A and 2B). The Worst Pruritus NRS (1.0) asks participants to rate how bad their itching has been in the last 24 h using a 0–10 NRS, with 0 representing no itch and 10 representing the worst itch imaginable. Version 2A of the Skin Pain NRS asks participants to rate their 'skin pain at the worst moment' during the last 24 h, while version 2B asks participants to rate their 'worst skin pain' during the last 24 h. Both versions of the AD Skin Pain NRS item include the same NRS from 0 (no skin pain) to 10 (worst skin pain imaginable). Based on direct feedback from the FDA subsequent to stage 1 content evaluation, the wordings were simplified to develop revised versions of both the Worst Pruritus NRS (1.1) and AD Skin Pain NRS (1.1). The simplified wording for the revised Worst Pruritus NRS (1.1) asks participants to rate their itching at its worst in the last 24 h; no modifications were made to the rating scale. The simplified wording for the revised AD Skin Pain NRS (1.1) asks participants to rate their skin pain at its worst in the last 24 h; no modifications were made to the rating scale.

Five measures were assessed in stage 2: the revised Worst Pruritus NRS (1.1), the revised AD Skin Pain NRS (1.1), two versions of the Sleep Disturbance NRS (A and B), the skin pain-specific PGIC and the skin pain-specific PGIS. The Sleep Disturbance NRS asks participants to rate how much of a problem sleep has been in the last 24 h due to AD. Both versions (A and B) of the Sleep Disturbance NRS use a 0–10 NRS scale, with '10 = I did not sleep at all'. However, the response scale for version A of the Sleep Disturbance NRS uses '0 = no sleep loss', while version B uses '0 = no sleep problems'. The skin pain-specific PGIC asks participants to rate their overall change in skin pain related to AD since they started taking the study medication using seven responses ranging from 'very much better' to 'very much worse'. The skin pain-specific PGIS asks participants to use four response options (none, mild, moderate, severe) to rate the severity of skin pain related to AD over the past week.

Results

Stage 1: Initial content evaluation of Worst Pruritus Numeric Rating Scale (NRS) and atopic dermatitis Skin Pain NRS

Participant demographic and clinical characteristics reported at screening are presented in Table 2. Across both rounds of interviews in stage 1 (round 1: $n = 8$ adults, 5 adolescents; round 2: $n = 8$ adults, 5 adolescents), a total of 26 individuals with moderate or severe AD [mean (SD) POEM score 16.3 (3.7)] participated in the initial content evaluation of the initial Worst Pruritus NRS (1.0) and initial AD Skin Pain NRS (1.0). The study sample in this stage included an equal number of female ($n = 13$) and male ($n = 13$) patients. The mean (SD) age of adult participants ($n = 16$) was 40.8 (9.6) years and the mean (SD) age of adolescent participants ($n = 10$) was 14.1 (11.7) years (range 12–17). The mean (SD) number of years since AD diagnosis for adults and adolescents was 14.1 (11.7) and 10.0 (5.6), respectively. The study sample in this stage included White ($n = 13/26$; 50%), Black ($n = 10/26$; 38%), Hispanic ($n = 2/26$; 8%) and Asian participants ($n = 1/26$; 4%). Half of the adults ($n = 8/16$; 50%) had a college or advanced degree, and just over half worked full time ($n = 9/16$; 56%).

Participant feedback during concept elicitation was consistent across all participants by round and by age. Figure 2 summarizes all the AD symptoms participants reported experiencing. As anticipated, all participants reported itch (pruritus) and skin pain. Table 3 summarizes the specific patient-reported experience with pruritus and skin pain. Tables 4 and 5 present representative quotes about participants' experiences with these symptoms and their impacts. Multiple participants reported that itch (pruritus) 'comes and goes' with varied severity and is disruptive to daily activities ['If I'm doing my work or something, and my leg starts itching, I'll just stop and itch it' (in-depth interview or 'IDI' 7)] and sleep ['…it'll wake me up in the middle of the night (because) it itches so bad' (IDI 5)]. Skin pain was described by multiple participants as a burning sensation and similarly reported to affect daily activities ['…if I'm flaring, and I'm having skin pain as a result of the flare, I limit my activities' (IDI 10)].

Using a scale from 0 (not at all bothersome) to 10 (extremely bothersome), participants rated their pruritus as

Table 2 Participant characteristics reported at screening for the initial content evaluation of Worst Pruritus Numeric Rating Scale (NRS) and atopic dermatitis (AD) Skin Pain NRS (stage 1)

Characteristic	Adults (*n* = 16)	Adolescents (*n* = 10)	Total (*n* = 26)
Sex			
Male	8 (50)	5 (50)	13 (50)
Female	8 (50)	5 (50)	13 (50)
Current age (years), mean (range)	40.8 (26–56)	14.1 (12–17)	30.5 (12–56)
Years since AD diagnosis (years), mean (range)	14.1 (2–40)	10.0 (1–17)	12.5 (1–40)
POEM score, mean (range)	16.0 (11–27)	16.7 (12–20)	16.3 (11–27)
Severity of AD-related pruritus[a]			
Mild	1 (6)	0 (0)	1 (4)
Moderate	7 (44)	4 (40)	11 (42)
Severe	8 (50)	6 (60)	14 (54)
Severity of AD-related skin pain[a]			
Mild	3 (19)	0 (0)	3 (12)
Moderate	8 (50)	5 (50)	13 (50)
Severe	5 (31)	5 (50)	10 (38)
Race			
White	9 (56)	4 (40)	13 (50)
Black	5 (31)	5 (50)	10 (38)
Asian	0 (0)	1 (10)	1 (4)
Other[b]	2 (12)	0 (0.0)	2 (8)
Ethnicity			
Hispanic	2 (12)	0 (0)	2 (8)
Non-Hispanic	14 (88)	10 (100)	24 (92)
Highest educational level[b]			
High school or GED	2 (12)	–	2 (12)
Technical or associate degree	2 (12)	–	2 (12)
Some college	4 (25)	–	4 (25)
College degree	5 (31)	–	5 (31)
Professional or advanced degree	3 (19)	–	3 (19)
Employment status[b]			
Student	1 (6)	–	1 (6)
Part-time	3 (19)	–	3 (19)
Full-time	9 (56)	–	9 (56)
Not employed/retired	3 (19)	–	3 (19)

Data are presented as *n* (%) unless otherwise stated. GED, General Educational Development; POEM, Patient Oriented Eczema Measure. [a]Participants were asked to rate the severity at its worst in the past 2 weeks as mild, moderate or severe. [b]Race or ethnicity not provided.

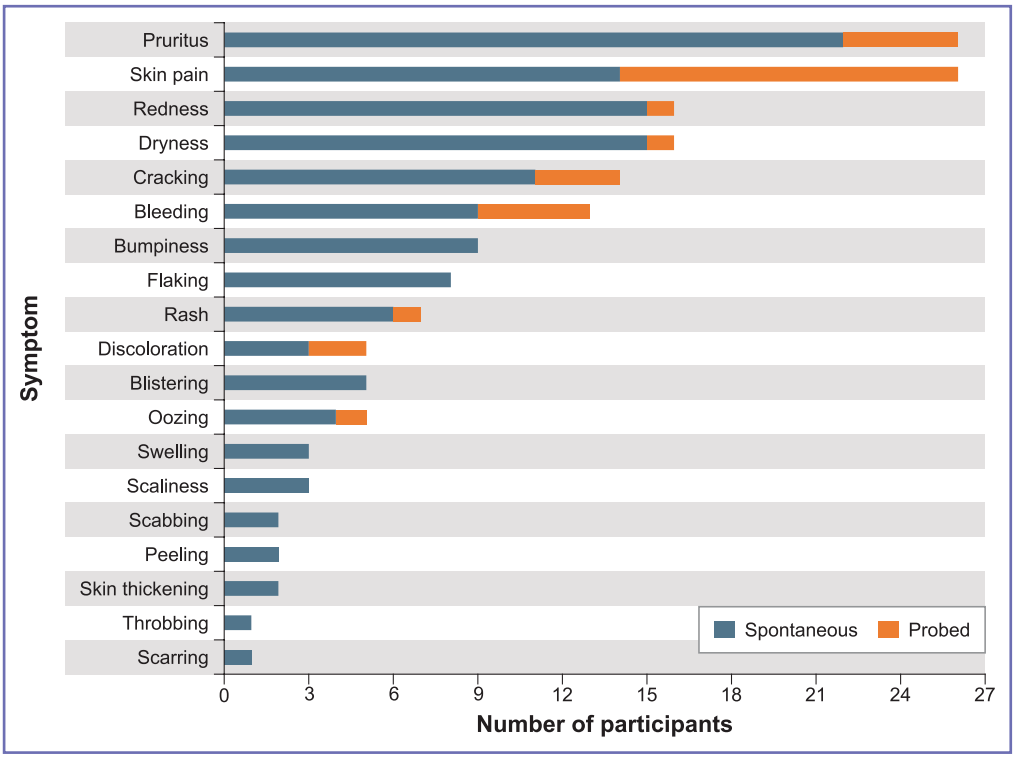

Figure 2 Participant-reported symptoms of atopic dermatitis.

Table 3 Participant ($n = 26$) experiences with atopic dermatitis (AD)-related pruritus and skin pain

AD symptom	*n* (%)
Pruritus	
Experienced pruritus	26 (100)
Experienced pruritus intermittently	22 (85)
Sweating makes pruritus worse	18 (69)
Reported pruritus was worse at night	17 (65)
Pruritus impacts daily activities[a]	15 (58)
Being outdoors, particularly during warmer weather, makes pruritus worse	14 (54)
Showering or washing, rinsing, or soaking their hands or face makes pruritus worse	10 (38)
Skin pain	
Experienced skin pain	26 (100)
Experienced skin pain intermittently	23 (88)
Being outside in the sun and/or sweating makes skin pain worse	18 (69)
Scratching makes skin pain worse	15 (58)
Reported skin pain was worse at night	14 (54)
Skin pain impacts daily activities[a]	11 (42)
Friction – caused, for example, by wearing clothes or jewellery, by being under bedsheets, or holding a dog leash – makes skin pain worse	10 (38)

[a]Daily activities include working, schoolwork, exercising, playing sports and socializing.

a mean (SD) of 7.0 (1.6) and skin pain as a 6.6 (2.0), indicating a high burden level for both symptoms. Additional symptoms commonly reported by participants included skin redness ($n = 16/26$; 62%), dryness ($n = 16/26$; 62%), cracking ($n = 15/26$; 58%) and bleeding ($n = 13/26$; 50%) (Figure 2).

During cognitive debriefing, no modifications were made to the initial Worst Pruritus NRS (1.0) and the two initial AD Skin Pain NRS (1.0) item versions (2A and 2B) after either round. Participants were shown a single PROM at a time, asked to read the instructions aloud and prompted to provide feedback ('Tell me, in your own words, what the instructions mean to you'), and then asked to read the item aloud and provide feedback ('Is there anything confusing about this question?') before proceeding to the next PROM. Table 6 contains representative quotes from the cognitive debriefing. All participants reported that the instructional text was clear and easy to understand, all participants generally defined 'the last 24 hours' consistently and accurately, and all participants reported the NRS as clear and easy to use to select a response. While the majority ($n = 21/26$; 81%) reported their understanding of the initial Worst Pruritus NRS item (1.0) as clear and interpreted it as intended ['In the last 24 hours, rate the worst your itching has been' (IDI 3)], five participants initially misinterpreted the item as asking about their average pruritus (one adolescent and two adults in round 1) or an overall general rating of their pruritus rather than their worst itch in the last 24 h (one adolescent in round 1 and one adult in round 2). Additionally, two adult and two adolescent participants in round 2 initially interpreted the item as intended but, when asked to explain what they were thinking about when they selected an answer, reported responding to the item with a general rating of their AD-related itch (instead of worst itch) in the last 24 h. Accordingly, additional instructions were developed for patient training on completion of this item for future clinical trials.

All participants reported that both initial AD Skin Pain NRS (1.0) items were clear and interpreted 2A as intended, with 20 of 26 (77%) reporting that these two items were asking the same question (i.e. asking participants to rate their worst skin pain in the last 24 h). However, 18 of 26 participants (69%) reported that AD Skin Pain NRS (1.0) item 2A was clearer than item 2B ['I think that 2A is easier because it asks you to pinpoint a specific moment' (IDI 15)], and 6 of 26 participants (23%) misinterpreted 2B by reporting that item

Table 4 Representative quotes from individuals with atopic dermatitis (AD) with regard to pruritus and skin pain symptoms

AD symptom	Representative symptom experience quotes
Pruritus	• 'It comes and goes, and sometimes it's worse than other times. Sometimes it will only itch a little bit, but if I've been active and sweaty…it makes the itching a lot worse. Just daily activities. If I'm walking, and I start sweating or just any time I sweat. I don't specifically work out, but if I get hot, if I'm in the sun…anything that causes me to sweat' (IDI 2). • '[The itching] comes and goes. This week it's kind of been on my left arm on the elbow area, and it'll come and go. [It is] worse at night. When I'm in bed…it'll wake me up in the middle of the night [because] it itches so bad. [It happens] very sporadic[ally]; sometimes it won't happen for a few weeks, and then it will happen several times in a matter of a week. I have to get up 2 or 3 times and put on the ointment that the doctor has given me to try to calm it down and usually it's like the third application or something I can go back to sleep but it's just a horrible itch. I don't even know how to describe it. You want to rip your arm off' (IDI 5). • 'Yeah. [The itching] comes and goes. It itches a lot at night. It itches a little, and then when…I'm in my bed, it's just like I have to itch it' (IDI 8*). • 'Usually, it's itching…and that's how I know it's about…to flare up and get worse. But the itching is usually the start of everything. Sometimes [it will be] really severe, sometimes it's pretty mild, sensitive, slightly severe. Oh, [the itching] is just pretty much [always] there. I get sores a lot because I'm always scratching. I'm actually scratching right now' (IDI 21).
Skin pain	• '…If I start sweating, or I'm wearing something that's rubbing on me, I get the burning sensation. It just literally feels like fire. It comes and goes just like the itching does. If I have been scratching, [I get skin pain]. I think if I were to wear a tight tank top, and it didn't have a bra on, if something rubs on it, it makes it worse' (IDI 2). • 'Not painful, like a stabbing pain, [but] like a sharp scratch. [I feel it] maybe when I scratch too much, and [when] I try to bend my legs, it starts to hurt. The more I stretch my legs it hurt, [and] it starts to hurt when I scratch my legs. [I usually feel it] 3 times in 1 day. [It is worse during] the day' (IDI 7*). • 'Yeah. I think it's from itching more. If I itch a lot, then it'll start to hurt…on the back of my calf; [particularly], when my sock's rubbing on it from soccer. Then it will start to hurt after because something's rubbing on it constantly, like my socks. [Also, after] swimming [and] after showers…like after showers, you can tell that it hurts' (IDI 8*). • '[The skin pain is worse in] the heat [either] the temperature [outside or] sweating. If it's really hot, it just burns where I am scratching. If it gets to the point of where I'm scratching in the same place so much that I break my skin, then every time I scratch again after that, it hurts' (IDI 26*).

IDI ('in-depth interview') indicates participant number; an asterisk following the IDI number denotes an adolescent participant.

Table 5 Representative quotes from individuals with atopic dermatitis (AD) with regard to pruritus and skin pain impacts

AD symptom	Representative impact experience quotes
Pruritus	• 'If I'm doing my work or something, and my leg start itching, I'll just stop and itch it. And then when I'm done scratching it, I just go back to my work until it start itching. If I'm taking out the trash or something and washing dishes and maybe dusting the house. The dust triggers me so I just start itching. I just stop [what I'm doing]' (IDI 7*). • 'I can't do my work because the main place I break out at is my hands. It prevents me from writing, typing, and clicking things and focusing. …when my hands start to itch, I start scratching, and the itching throws off my concentration' (IDI 16*). • 'Maybe I'm in class, and I'm taking a test, and I just start scratching my arm, hand for a little while, and that's all I can think about at the moment. Well, it takes time away [from] the [test]' (IDI 26*).
Skin pain	• 'It does affect the day to day. For instance, if I'm flaring, and I'm having the skin pain as a result of the flare, I limit my activities. I don't go to the pool. I don't go to the gym. I don't want to do anything to make it worse, so I stop doing things. I really stop my activities' (IDI 10). • 'It limits what I enjoy doing because I do like to work with my hands so much, and I do like to take my dog on walks and go places. It's been preventing me from being able to do that as much as I'd like to do just because I can't physically make myself do some of those things for prolonged periods of time. A lot of times, I live with my partner, I'll ask him to go take the dog out or him to cook or he'll want to have people over, and I don't really want people over because my hands hurt or because it's gross looking' (IDI 17). • 'Yes, ma'am. My schoolwork, it [skin pain] just usually distracts me a lot from what I'm doing and when I have to do my work and stuff' (IDI 19*).

IDI ('in-depth interview') indicates participant number; an asterisk following the IDI number denotes an adolescent participant.

2B was asking them to rate their skin pain in general during the last 24 h. As a result, version 2A was selected as the AD Skin Pain NRS (1.0) version on the basis of stage 1 participant feedback. Subsequently, based on direct feedback from the FDA, the item wordings were both simplified, resulting in revised versions of the Worst Pruritus NRS (1.1) and AD Skin Pain NRS (1.1). Additional content evaluation with new participants was then conducted in stage 2 of the research.

Stage 2: Follow-up content evaluation of five patient-reported outcome measures for atopic dermatitis

Across both rounds of interviews in stage 2 (round 1: $n = 6$ adults, 4 adolescents; round 2: $n = 5$ adults, 6 adolescents), 21 individuals with moderate or severe AD [mean (SD) POEM score 17.2 (4.9)] participated (Table 7). The study sample in this stage included similar proportions of female ($n = 11$) and male ($n = 10$) participants. The mean (SD) age of adult participants ($n = 11$) was 42.3 (14.1) years and 14.2 (1.6) years in adolescent participants ($n = 10$). The interview sample in this stage was composed of Black ($n = 7/21$; 33%), White ($n = 7/21$; 33%), Hispanic ($n = 4/21$; 19%) and Asian participants ($n = 2/21$; 10%), as well as one participant who identified as White and Hispanic (5%). Approximately half of the adults had a college or advanced degree ($n = 5/11$; 45%) and worked full time ($n = 5/11$; 45%).

All items were debriefed with the full sample (11 adults and 10 adolescents) except for the Sleep Disturbance NRS version B (10 adults, 10 adolescents) and the skin pain-specific PGIC and PGIS items (11 adults, 9 adolescents), which were each debriefed with 20 participants. Table 8 contains representative quotes from debriefing for each of the five evaluated PROMs.

Table 6 Representative quotes from individuals with atopic dermatitis (AD) from the initial Worst Pruritus Numeric Rating Scale (NRS) and initial AD skin Pain NRS content evaluation (stage 1)

PROM component debriefing	Representative quotes
Instructional text (both PROMs)	• 'Just think about the areas where I have the issue and don't focus on anything else. I think that's pretty well-written for what we're talking about' (IDI 12). • 'Only to answer the questions based on the specific areas where you're experiencing the eczema. I think it's pretty straightforward' (IDI 15).
Worst Pruritus NRS Item (1.0)	• 'In the last 24 hours, rate the worst your itching has been' (IDI 3*). • 'To rate how bad the itching is at its worst in the last day' (IDI 15). • 'Within the last day, tell me how bad your itching has been at its worst' (IDI 17).
AD Skin Pain NRS Item (1.0) (version 2A)	• '…How I would rate it if it was the worst skin pain [that] I had within the last 24 hours' (IDI 7*). • 'My skin pain in the last 24 hours. [My] worst skin pain' (IDI 8*). • 'To rate your skin [pain] at the worst in the last 24 hours' (IDI 9*).
AD Skin Pain NRS Item (1.0) (version 2B)	• 'I mean, it's asking me to describe how painful that pain is in the last 24 hours' (IDI 15). • 'This question is asking me what's the worst skin pain…what skin pain was the most intense in the last 24 hours, and how will I rate my skin pain' (IDI 16*). • 'To rate your worst skin pain in the last day' (IDI 26*).
Comparing AD Skin Pain NRS versions 2A and 2B	• 'I think that 2A is easier because it asks you to pinpoint a specific moment. That moment is when I've scratched it so much that it starts bleeding. For me, personally, that's what I would think of, and it helps me to kind of pinpoint that specific time frame versus just looking at a 24 hour period when the skin pain was the worst' (IDI 15). • '2A [is clearer] because it's saying your worst moment during the last 24 hours' (IDI 19*).

IDI ('in-depth interview') indicates participant number; an asterisk following the IDI number denotes an adolescent participant. PROM, patient-reported outcome measure.

Table 7 Participant characteristics reported at screening for follow-up content evaluation of five atopic dermatitis (AD) patient-reported outcome measures (stage 2)

Characteristic	Adults ($n = 11$)[a]	Adolescents ($n = 10$)[b]	Total ($n = 21$)
Sex			
Male	5 (45)	5 (50)	10 (48)
Female	6 (55)	5 (50)	11 (52)
Current age (years), mean (range)	42.3 (19–61)	14.2 (12–17)	28.9 (12–61)
POEM score, mean (range)	17.0 (10–23)	17.5 (9–28)	17.2 (9–28)
AD severity[c]			
Moderate	5 (45)	5 (50)	10 (48)
Severe	6 (55)	4 (40)	10 (48)
Very severe	0 (0)	1 (10)	1 (5)
Race/ethnicity			
White	4 (36)	3 (30)	7 (33)
Black	3 (27)	4 (40)	7 (33)
Asian	1 (9)	1 (10)	2 (10)
Hispanic	2 (18)	2 (20)	4 (19)
Mixed race/ethnicity[d]	1 (9)	0 (0)	1 (5)
Highest educational level[e]			
High school or GED	4 (36)	–	4 (19)
Technical or associate degree	2 (18)	–	2 (10)
College degree	4 (36)	–	4 (19)
Professional or advanced degree	1 (9)	–	1 (5)
Employment status[e]			
Part-time	3 (27)	–	3 (14)
Full-time	5 (45)	–	5 (24)
Not employed/retired	1 (9)	–	1 (5)
Self-employed	2 (18)	–	2 (10)

Data are presented as *n* (%) unless otherwise stated. Owing to rounding, not all percentages total 100%. GED, General Educational Development; POEM, Patient Oriented Eczema Measure. [a]One adult in round 1 was not shown the revised Sleep Disturbance Numeric Rating Scale version B, so another adult participant was added. [b]One adolescent participant did not have time to provide feedback on the skin pain-specific Patient Global Impression of Severity or Patient Global Impression of Change. [c]AD severity classification was based on POEM score (8–16 = moderate; 17–24 = severe; 25–28 = very severe). [d]One adult participant reported being both White and Hispanic. [e]Applicable to adults and not adolescents.

Table 8 Representative quotes from individuals with atopic dermatitis (AD) from follow-up content evaluation of five atopic dermatitis (AD) patient-reported outcome measures (stage 2)

PROM component debriefing	Representative quotes
Instructional text (revised Worst Pruritus NRS 1.1 and revised AD Skin Pain NRS 1.1)	• 'They're quite clear, just your regular skin should not be included. Like my face is, I don't have eczema on my face so it's not included in the answer' (IDI 6*). • 'It's simple and very direct and gets straight to the point. Describe my eczema' (IDI 10*).
Revised Worst Pruritus NRS item 1.1	• 'How it wants me to rate, how bad it itches, how bad the eczema patch itches' (IDI 20). • 'Just how itchy have you been, how at its worst during the last, the past day?' (IDI 6*). • 'To rate how much your skin itches at its worst from the past 24 hours' (IDI 12*).
Revised AD Skin Pain NRS item 1.1	• 'It's just saying, the past day, what's the most your skin has been hurting, basically' (IDI 17). • 'Rate the pain of your skin in the last 24 hours' (IDI 16*). • 'It's asking me to say how much pain I've had due to my eczema within the last day' (IDI 18*).
Sleep disturbance NRS item (version A)[a]	• 'Yes, it's asking me, has my eczema in the last 24 hours caused any sleep disturbances for me, have… did I get lack of sleep perhaps due to my eczema, so fairly easy to understand' (IDI 3). • 'Asking me if I've had any issues with my sleeping due to my eczema' (IDI 11). • 'How much did your eczema prevent you from sleeping in the last day?' (IDI 7*).
Comparing sleep disturbance NRS items from versions A and B	• 'You can have some sleep problems, but you can still end up going to sleep. […] Maybe you can have sleep loss without having sleep problems. I'm not sure where I'm going with that, but they're a little bit different, but I wouldn't say too much of a difference actually' (IDI 17). • 'I prefer the first question [sleep disturbance NRS version A "no sleep loss"]. To me, it kind of zeros in on the information that you're trying to get better. It just hits home quicker and it's very, a lot clearer to me and so I don't have to stop and think about the question itself. After I read it, I understand it and then I can go on to thinking about the answer to the question' (IDI 9).
Skin pain-specific PGIC	• 'To think about the change, the overall change within my skin pain due to my eczema since I started taking this new study medication' (IDI 3). • 'How much did your skin pain change since you started taking medicine for it?' (IDI 7*).
Skin pain-specific PGIS	• 'This is asking me to think back over the past 7 days, to pick a response that best describes how severe my pain was, my skin pain related to my eczema' (IDI 2). • 'Choose a response that describes the pain of your skin from the last week' (IDI 16*). • 'It's asking me to say how much pain I've been over the past week due to my eczema' (IDI 18*).

IDI ('in-depth interview') indicates participant number; an asterisk following the IDI number denotes an adolescent participant. PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; NRS, Numeric Rating Scale. [a]Representative quotes are from review of version A; the majority of participants ($n = 19/20$) also reported that version B was clear.

Revised Worst Pruritus Numeric Rating Scale (NRS) and revised atopic dermatitis Skin Pain NRS

The 21 participants who reviewed the revised Worst Pruritus NRS (1.1) and revised AD Skin Pain NRS (1.1) reported that the instructional text for the items was clear and easy to understand, and all interpreted the text consistently. They also reported that these items and their respective response options were clear and easy to use (Table 8). In addition, all participants were able to provide interpretations of the meanings of selected numbers on the Worst Pruritus NRS ['My itching hasn't been bad. (…) It's been like a minor itch. So I will just rate it a 3' (IDI 6)] and AD Skin Pain NRS ['I would say like a 9 because it was burning really bad' (IDI 19)]. Consequently, no modifications were made after either interview round and the revised Worst Pruritus NRS (1.1) and revised AD Skin Pain NRS (1.1) items were maintained as the final items.

Sleep Disturbance Numeric Rating Scale

Across both rounds of interviews, 20 of the 21 participants who reviewed the Sleep Disturbance NRS version A reported that it was clear and consistently interpreted the item as intended (Table 8). One adolescent from round 2 reported that the question was confusing to understand because she did not experience itch while asleep. However, she was still able to select a response to the item as written that reflected her experience. All participants were able to provide interpretations of the meanings of selected numbers on the NRS. Across both rounds, 19 of the 20 participants who reviewed the Sleep Disturbance NRS version B reported that this version of the item was clear and the alternative 0–10 scale was easy to use to select a response. One adult from round 1 reported that, at first, it was a bit hard to select a response that reflected his experience, but this participant was ultimately able to do so.

No modifications were made to either Sleep Disturbance NRS item (version A or B) after either interview round. When selecting an answer on either item version, participants generally thought about AD symptoms (e.g. itch and skin pain) that caused them difficulty falling asleep and/or woke them up during the previous night. Participants were additionally asked to indicate the amount of change on the Sleep Disturbance NRS they would consider a meaningful improvement ['You selected (respondent's highest value); using the scale provided, what is the amount of improvement in sleep that you would consider meaningful?']. The median amount of change on either version that would be considered a meaningful improvement in sleep was 4.5 (range 1–10) [$n = 21$; mean (SD) 4.8 (1.8)] across the sample. Version A was reported by 12 of 20 participants (60%) to best capture the impact of AD on sleep ['I prefer the first question (sleep disturbance NRS version A "no sleep loss"). To me, it kind of zeros in on the information that you're trying to get better' (IDI 9)]; therefore, version A was recommended as the final Sleep Disturbance NRS item.

In addition to cognitive debriefing of the Sleep Disturbance NRS item, participants were queried and probed further during an abbreviated concept elicitation regarding the relevance and importance of evaluating sleep disturbance due to AD (Table 9). Nearly all participants across both rounds of interviews indicated that problems with sleep were both relevant to their experience with AD ($n = 18/20$; 90%) and important to measure ($n = 20/21$; 95%) in reported sentiments, such as 'Sleep is very important. I think, just common you need sleep when you're dealing with kids or going to work and when I'm short on sleep because of my eczema, I lack during the day' (IDI 4). The sleep impacts spontaneously reported most often were night-time wakening [$n = 14$; 'I'm tossing and turning all night and scratching' (IDI 13)] and trouble falling asleep [$n = 7$; '(…) if it's itching bad and I lay there for, I'm not going to say hours on end, but lay there an

Table 9 Representative quotes from individuals with atopic dermatitis (AD) about AD-related sleep disturbance

Aspect	Representative quotes
Relevance and importance	• 'The sleep is very relevant for me. If I get a good night's sleep and I don't get a good night's sleep, that changes my whole mood and attitude throughout the whole day. When I don't get a good night's sleep, it's hard for me to function, I have a bad attitude. I'm not energised. And I'm just intolerant more' (IDI 1). • 'Sleep is very important. I think, just common you need sleep when you're dealing with kids or going to work and when I'm short on sleep because of my eczema, I lack during the day' (IDI 4). • 'I think so because it [eczema] affects everything about the sleep' (IDI 18*).
Night-time wakening	• 'I wake up a lot. I never used to wake up much, but certain times a year when it affects me more, I don't sleep as well. And that causes problems for me at work, at home, not being the same person that I usually am' (IDI 1). • 'When my eczema is very itchy, and I wake up at the middle of the night, I just go to the bathroom and just wash my skin down so it could cool off' (IDI 12*). • 'I'm tossing and turning all night and scratching. And that's very uncomfortable' (IDI 13).
Trouble falling asleep	• 'The goal is to try to get sleep and when I get ready to go to bed and if it is, if I'm, if it's itching bad and I lay there for, I'm not going to say hours on end, but lay there an hour or 2 itching' (IDI 9).
Feeling unrested upon wakening	• 'I don't feel good throughout the day. I don't get the restorative sleep that I need for my body to feel better. Mentally and physically' (IDI 1). • 'Yeah, [I] do wake up feeling tired sometimes' (IDI 7*).
Early-morning wakening	• 'Well, yeah sometimes. It doesn't wake me up like…it wakes me up sooner before. Like hours before' (IDI 16*). • 'Today, I did because remember when I told you about the scratches. I woke up early because of that and then I showed my mom' (IDI 19*).
Insufficient amount of sleep	• 'If I have a flare-up is usually when I have… . I don't get very much sleep at night' (IDI 4).

IDI ('in-depth interview') indicates participant number; an asterisk following the IDI number denotes an adolescent participant.

hour or 2 itching. (IDI 9)] (Tables 9, 10). Upon further probing of all potential sleep impacts, night-time wakening was still most frequently reported ($n = 20$), followed by feeling unrested upon awakening ($n = 19$), insufficient amount of sleep ($n = 17$), early-morning awakening ($n = 16$) and trouble falling asleep ($n = 14$) (Table 10). The top three sleep impacts reported as most bothersome were trouble falling asleep ($n = 8$), followed by night-time wakening ($n = 5$) and feeling unrested upon awakening ($n = 4$). Itch ($n = 21$) and skin pain ($n = 3$) were the AD-related symptoms participants most frequently reported as affecting their sleep.

Skin pain-specific Patient Global Impression of Change

Across both rounds of interviews, all 20 participants who reviewed the skin pain-specific PGIC reported that this item was clear and interpreted it as intended (Table 8). All 20 participants also reported that the response options for the skin pain-specific PGIC were clear and easy to use to select a response when thinking about the last medication they used to treat their skin pain (as no participants were taking a study medication). In addition, all participants were able to provide interpretations of the meanings of each of the response options [e.g. '(Very much better) I forget that I have eczema' (IDI 4); 'A little worse would be that the medication isn't doing anything. It's just making my skin feel a little bit more pain' (IDI 12)]. Consequently, no changes were made to this item, and the version tested was maintained as the final skin pain-specific PGIC. The majority of participants reported that an improvement in their skin pain of 'much better' ($n = 11$) or 'very much better' ($n = 7$) with a new AD treatment would be meaningful.

Skin pain-specific Patient Global Impression of Severity

Across both rounds of interviews, all 20 participants who reviewed the skin pain-specific PGIS reported that this item was clear and interpreted it as intended (Table 8). All 20 participants also reported that the response options for the skin pain-specific PGIS were clear and easy to use and interpreted them as intended; thus, no changes were made, and the version tested was maintained as the final skin pain-specific PGIS. When probed, the majority ($n = 15/20$; 75%) of participants indicated that a 1-point change on the response scale would be a meaningful improvement in their skin pain with a new treatment [e.g. 'I think moving one level on the scale. I would consider that meaningful. If you were severe and you got knocked down to a moderate, or if you were a moderate got down to mild, or mild got down to none' (IDI 1)].

Discussion

The findings from this qualitative study provide evidence that supports the content validity of the revised Worst Pruritus NRS (1.1), revised AD Skin Pain NRS (1.1), the Sleep Disturbance NRS (A and B), the skin pain-specific PGIC and the skin pain-specific PGIS in individuals aged ≥ 12 years with moderate-to-severe AD. Results were generally aligned and consistent for adult and adolescent participants. Additionally, we confirmed that sleep disturbance is a relevant and important concept for evaluation in adults and adolescents with moderate-to-severe AD, while also providing further confirmation of this for pruritus and skin pain. The most frequently reported sleep impacts included night-time wakening, feeling unrested upon wakening and an insufficient amount of sleep, while participants were most bothered by trouble falling asleep, night-time wakening and feeling unrested upon wakening.

Participants found the initial Worst Pruritus NRS (1.0) and AD Skin Pain NRS (1.0) items and corresponding instructional text clear and easy to understand. However, owing to misinterpretation of the initial Worst Pruritus NRS (1.0) by 19.2% of interview participants, development of further instructions for patient training on completion of the original item was deemed necessary to reduce the potential for variability in responses across clinical trial participants. Furthermore, in response to FDA feedback, the wording of the initial Worst Pruritus NRS (1.0) and AD Skin Pain NRS (1.0) items was simplified to increase readability and comprehension. All participants who reviewed the revised Worst Pruritus NRS (1.1), the revised AD Skin Pain NRS (1.1), the skin pain-specific PGIC and the skin pain-specific PGIS reported that these items and their respective response options were clear and easy to use, and interpreted them as intended. Consequently, no modifications were made to any of these four items after either interview round. Nearly all adolescent and adult participants reported that the question wording for the Sleep Disturbance NRS (versions A and B) was clear and interpreted it consistently as intended. However, version A of the Sleep Disturbance NRS was reported by a majority of the sample as best at capturing

Table 10 Impact of atopic dermatitis on sleep reported by study participants

	Participant no.																						
Activity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**MB**	**Total**
Night-time wakening	S	S	S	S	–	P	P	S	S	S	P	P	S	S	S	S	S	P	S	S	P	5	20
Feeling unrested upon wakening	P	P	–	P	P	P	P	P	P	P	P	–	P	P	P	P	P	P	S	P	P	4	19
Insufficient amount of sleep	P	P	–	P	–	P	P	P	P	P	P	–	P	P	P	P	P	-	S	S	P	3	17
Early-morning wakening	P	P	–	P	P	P	–	–	P	P	P	–	S	P	P	P	P	-	P	P	P	1	16
Trouble falling asleep	–	P	S	–	–	S	S	S	–	–	P	P	S	–	–	S	P	P	S	P	P	8	14

MB, most bothersome; P, probed; S, spontaneous.

the impact of AD on sleep and was recommended as the final response scale for this item.

By providing a deeper understanding of patients' experience with AD, these five new measures add further value to the instruments currently endorsed by Harmonising Outcome Measures for Eczema (HOME). The HOME Core Outcome Set (COS) for evaluating AD in clinical trials includes instruments that assess four key domains:[19] patient-reported symptoms (POEM and Peak Pruritus NRS);[20,21] extent and severity of AD (EASI);[12] AD control [Recap of atopic eczema (Recap) or Atopic Dermatitis Control Test (ADCT)];[22,23] and quality of life (Dermatology Life Quality Index).[24–26] Although the COS assesses critically important outcomes, the findings of our research suggest that the inclusion of additional measures may be needed to improve our understanding of the patient experience of living with AD and the resulting effects of treatments. While the patient experience reflected in the interviews demonstrated that peak skin pain and sleep disturbance are relevant and important dimensions of the AD experience, no measures in the COS collect patient-reported information in these domains. HOME has also acknowledged that the use of single-item measures for specific domains, such as sleep loss, should be considered.[19] Similarly, the Peak Pruritus NRS collects outcomes on peak AD-related pruritus over the previous 24 h. However, the revised Worst Pruritus NRS differs from the Peak Pruritus NRS in that it measures the same concept using simpler wording, which may further optimize patient comprehension and reduce data variability when included in clinical trials evaluating treatment for moderate-to-severe AD. Finally, the skin pain-specific PGIS and skin pain-specific PGIC are anchor measures anticipated to support the evaluation of meaningful score differences on the AD Skin Pain NRS. These types of anchor measures are considered by regulatory authorities as valuable for inclusion in clinical trials in order to support interpretation of the clinical outcome assessments measuring the same concept (i.e. AD Skin Pain NRS), which are anticipated to support key trial endpoints.[27]

A limitation applicable to this research was the inclusion of only English-speaking US participants who reported experiencing AD-related pruritus and skin pain (and sleep disturbance for stage 2). Other limitations included the small number of participants with an Asian background and that data about the skin type of participants were not collected. As this sample may not be generalizable to the larger population of people with AD, future research should recruit participants with more diverse backgrounds and employ a wider recruitment strategy to include participants from hospital dermatology clinics and community settings. The generalizability of the findings presented here could be further investigated through workshops. A limitation of stage 2 was the amount of time available with each participant to complete the cognitive debriefing of five AD PROMs. While all participants completed debriefing for the revised Worst Pruritus NRS and revised AD Skin Pain NRS, and for version A of the Sleep Disturbance NRS, only 20 of 21 participants had time to complete debriefing of version B of the Sleep Disturbance NRS, the skin pain-specific PGIC and the skin pain-specific PGIS. However, findings were consistent across all participants, including adolescents and adults.

While this research reports valuable PROM content evaluation from the perspective of adults and adolescents with moderate-to-severe AD, additional evaluations for comprehensive validation may be beneficial. While additional psychometric evaluation of the Worst Pruritus NRS was deemed unnecessary by the FDA, planned psychometric evaluation of the AD Skin Pain and Sleep Disturbance NRS items (e.g. test–retest reliability, construct validity and known-groups validity) and the assessment of the items' responsiveness in a phase III clinical trial setting combined with these qualitative study findings may be used to provide further evidence that these measures are fit-for-purpose in individuals aged ≥ 12 years with moderate-to-severe AD.

Our findings support the content validity of the revised Worst Pruritus NRS (1.1), revised AD Skin Pain NRS (1.1), Sleep Disturbance NRS, skin pain-specific PGIC and skin pain-specific PGIS in individuals aged ≥ 12 years with moderate-to-severe AD. Furthermore, the findings support sleep disturbance as being a relevant and important concept for adolescents and adults with moderate-to-severe AD, while also providing further confirmation of the same for pruritus and skin pain.

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Conflicts of interest

A.B. has served as a speaker (received honoraria) for AbbVie, Bristol Myers Squibb, Eli Lilly, Pfizer, Regeneron and Sanofi; served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris Therapeutics, Affibody, ALIGOS Therapeutics, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis Biotherapeutics, Arena, ASLAN Pharmaceuticals, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly, Escient Pharmaceuticals, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos Biopharma, LEO Pharma, Lipidio Pharma, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Pfizer, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome Therapeutics and Xencor; and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, ACELYRIN, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert,

Dermavant, Eli Lilly, Evelo, Evommune, Galderma, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB Pharma and Ventyx. J.R. was an employee of Amgen Inc., and may hold shares and/or stock options in the company. Y.Z. was an employee of Kyowa Kirin, Inc., and may hold shares and/or stock options in the company. E.E. is an employee of Kyowa Kirin, Inc., and may hold shares and/or stock options in the company. M.C., K.K., N.H., S.M. and D.W. are full-time employees of RTI Health Solutions, an independent nonprofit research organization, which was retained by Amgen Inc., to conduct the research that is the subject of this manuscript. Their compensation is unconnected to the studies on which they work. E.G.-Y. is an employee of Mount Sinai and has received research grants from Boehringer Ingelheim, LEO Pharma, Pfizer, Cara Therapeutics, UCB, Kyowa Kirin, RAPT, Amgen, GSK, Incyte, Sanofi, Bristol Myers Squibb, ASLAN Pharmaceuticals, Regeneron, AnaptysBio, Concert and Janssen; and is a consultant for AbbVie, Almirall, Amgen, ASLAN Pharmaceuticals, AstraZeneca, Biologic, Design, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Connect, Pharma, DBV Technologies, Eli Lilly, EMD Serono, Evidera, Galderma, Gate Bio, Genentech, Incyte, Inmagene Bio, Janssen Biotech, Kyowa Kirin, LEO Pharma, Merck, Pfizer, Q32 Bio, RAPT, Regeneron, Sanofi, SATO, Siolta, Target, UCB and Ventyx.

Data availability

Data are primarily in the form of transcripts and cannot be made available in order to protect participant privacy in accordance with the principles of the Belmont Report.

Ethics statement

The RTI Institutional Review Board reviewed the study materials and provided expedited approval for this research (STUDY00021209).

Patient consent

Participants provided consent for publication of deidentified findings. For all interviews, informed consent (for adults) or caregiver permission and child assent (for adolescents) was obtained prior to participation.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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