

# A qualitative interview study to explore adolescents' experience of alopecia areata and the content validity of sign/symptom patient-reported outcome measures\*

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## Summary

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Eli Lilly and Company, a pharmaceutical company, funded Clarivate (formerly DRG Abacus) to conduct this study. Clarivate a provider of insights and analytics to pharmaceutical companies, universities, nonprofits, funding organizations, publishers, corporations, government organizations and law firms.

### Conflicts of interest

J.M., H.K. and N.V.J.A. are employees and stockholders of Clarivate, providing specialised clinical outcome assessment and patient-centred outcomes consultancy to various pharmaceutical and medical device companies. E.E.-H., R.B. and A.P. are employees and stockholders at Eli Lilly and Company. B.A.K. has served on advisory boards and is a consultant and clinical trial investigator for Eli Lilly and Company, and has served on advisory boards and/or is a consultant and/or is a clinical trial investigator for Abbvie, Aclaris Therapeutics Inc., Almirall, AltruBio Inc., Arena Pharmaceuticals, Bioniz Therapeutics, Bristol-Meyers Squibb, Concert Pharmaceuticals Inc., Dermavant Sciences Inc., Eli Lilly and Company, Incyte Corp., LEO Pharma, Otsuka/Visterra Inc., Pfizer Inc., Regeneron, Sanofi Genzyme, TWi Biotechnology Inc. and Viela Bio. He is on speaker bureaus for Pfizer Inc., Regeneron and Sanofi Genzyme. N.M. has received honoraria/fees for advisory work with Eli Lilly.

**Background** The content validity (appropriateness and acceptability) of patient-reported outcome (PRO) measures for scalp hair loss, eyebrow loss, eyelash loss, nail damage and eye irritation has been demonstrated in adults with alopecia areata (AA) but not adolescents.

**Objectives** To explore the content validity of the suite of AA PRO measures and accompanying photoguides in an adolescent sample.

**Methods** Semi-structured, 90-min, combined concept elicitation and cognitive interviews were conducted face-to-face with adolescents who experienced  $\geq 50\%$  AA-related scalp hair loss. Transcripts underwent thematic and framework analysis.

**Results** Eleven adolescents (aged 12–17 years, 55% female, 45% nonwhite) diagnosed with AA for 5.9 years (mean) participated. Participants had 69.6% scalp hair (mean) and current eyebrow (82%) and/or eyelash loss (82%) and/or nail involvement (36%). Adolescents reported scalp, eyebrow and eyelash hair loss as their top three most bothersome signs/symptoms. Despite mostly accepting their AA, impacts related to visible areas of hair loss were prominent. Participants demonstrated good understanding and appropriate use of the PRO measures, and advocated including hair loss percentages alongside descriptive categories in the Scalp Hair Assessment PRO<sup>TM</sup>. Results confirmed treatment success thresholds established with adults: achievement of  $\leq 20\%$  scalp hair loss, no/minimal eyebrow and eyelash loss, no/a little nail damage and eye irritation (PRO measure categories 0 or 1).

**Conclusions** The Scalp Hair Assessment PRO<sup>TM</sup>, PRO Measure for Eyebrows<sup>TM</sup>, PRO Measure for Eyelashes<sup>TM</sup>, PRO Measure for Nail Appearance<sup>TM</sup> and PRO Measure for Eye Irritation<sup>TM</sup> and accompanying photoguides are fit-for-purpose self-reported measures of AA signs/symptoms that are impactful to adolescents with AA.

## Data availability statement

The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality of the information. However, the corresponding author can be contacted for any data-related questions.

\*Plain language summary available online

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Extensive evidence supports alopecia areata (AA) as a significant medical condition associated with emotional and psychosocial distress, including high prevalence of depression and anxiety.<sup>1–5</sup> AA involves scalp, facial and body hair loss and can cause nail damage (pitted, brittle nails),<sup>6–8</sup> all signs/symptoms associated with significant impairment of health-related quality of life.<sup>9–15</sup> The clinical signs of AA, including scalp hair loss, are time-consuming and often impossible to hide, resulting in patients being perceived as sick, if not gravely ill.<sup>9,16–22</sup>

The World Health Organization defines adolescence as ages 10–19 years, between childhood and adulthood.<sup>23</sup> The definition of adolescence varies across published AA studies but was defined as ages 12–17 years within this study. Although children and adolescents with AA exhibit positive attitudes and acceptance of their disease, adolescents may be less accepting of their AA, experience lower levels of confidence and self-esteem and be less social than children.<sup>24</sup> Indeed, adolescents with AA have reported bullying, feelings of embarrassment and limiting involvement in activities because of their AA; they also worry about the effects of AA on their parents and hide bullying from their parents.<sup>25</sup> Additionally, adolescents with AA have described feelings of isolation, self-consciousness or paranoia about judgement from others, loss of identity ('it's not just hair'), assumptions about their health status (e.g. hair loss associated with cancer) and uncertainty, fear and helplessness related to the unpredictability of their hair loss.<sup>18</sup>

The US Food and Drug Administration (FDA) has recognized the need for efficacious AA therapies because of the substantial emotional and psychological impact of the disease.<sup>19</sup> The development of novel therapies should be patient-focused and incorporate patients' experiences and priorities for treatment outcomes.<sup>26,27</sup> Comprehensive measurement of the patient experience of AA should assess signs/symptoms and the impact on how patients feel and function. A conceptual model of the experience of AA developed prior to this study<sup>9</sup> can be used by researchers to select or develop fit-for-purpose impact measures.

To assess key signs/symptoms in clinical practice and clinical studies, content-valid and clinically meaningful patient-reported outcome (PRO) measures for the assessment of scalp hair loss, eyebrow loss, eyelash loss, nail damage and eye irritation<sup>28,29</sup> have been developed for adults with AA in line with FDA guidance and best practice.<sup>26,27,30–32</sup> Corresponding clinician-reported outcome measures have also been developed<sup>29,33</sup> for comprehensive measurement of patients' key

signs.<sup>9,28,29</sup> Although, like adults, adolescents (aged 12–17 years as typically defined in clinical trial populations) are generally able to self-report, careful consideration should be given to differences in disease experiences and priorities and level of comprehension across adolescent age groups during PRO measure development.<sup>34,35</sup> Five adolescents (aged 15–17 years) were involved in the initial development of the AA PRO measures but subsequent revisions and accompanying photoguides developed for the eyebrow loss, eyelash loss and nail damage measures were confirmed with adults only.<sup>9,10,28,29</sup> Thus, evidence of the content validity (i.e. appropriateness and acceptability) of these measures was needed in an adolescent AA population. Additionally, acceptability of established treatment success thresholds required exploration;<sup>28,33,36</sup> in particular, achievement of near-complete scalp hair regrowth [ $\leq 20\%$  missing hair/Severity of Alopecia Tool (SALT) score  $\leq 20$ ] for those with  $\geq 50\%$  missing hair (SALT score 50–100).

This cross-sectional, noninterventional, qualitative concept elicitation and cognitive interview study aimed to explore experiences of adolescents with AA and whether the AA PRO measures and accompanying photoguides were fit-for-purpose in an age-diverse sample of adolescents with AA.

## Patients and methods

### Qualitative approach and research perspective

This study was designed to understand the adolescent experience of AA signs/symptoms and to explore the content validity of AA PRO measures through methodology informed by FDA PRO Guidance for Industry.<sup>26,30</sup>

### Context of the research

Semi-structured combined concept elicitation and cognitive interviews were conducted face to face at the adolescent patients' clinical site or a nearby meeting room in October 2019 and February 2020 by experienced, trained qualitative researchers (J.M. and N.V.J.A.). No interim changes were made to the interview guide; Table S1 (see Supporting Information) shows example questions. Parent/guardians attended the interview location and, with the adolescent patient, chose whether or not to sit in during the interview. Interviews lasted approximately 90 min; audio recordings were transcribed verbatim.

## Concept elicitation

Concept elicitation<sup>32</sup> comprised open-ended and probing questions that enabled patients to describe their experience of AA signs/symptoms and associated impacts and explored patients' methods for quantifying the amount of scalp hair loss and their perceptions of meaningful treatment improvement. Questions were based on a conceptual model of the effects of AA, developed from previous interviews with adults and adolescents.<sup>9</sup> Structured tasks, inspired by those used with school children of a similar age in the UK, were included to determine understanding of percentages; patients were asked to:

- Describe/define understanding of percentage
- Complete two graphical percentage tasks (Figure 1)
  - What percentage of a 10-slice pizza was missing after four slices had been taken away?
  - What percentage of a T-shaped graphic, designed to be an abstract representation of the scalp, was not coloured in?
- Provide an estimate of current percentage of missing scalp hair

## Cognitive debriefing

Cognitive debriefing<sup>31</sup> of the following single-item AA PRO measures<sup>28,29</sup> was designed to determine appropriateness (relevance) and acceptability of the measures using 'think aloud' methodology and specific probes.<sup>37</sup>

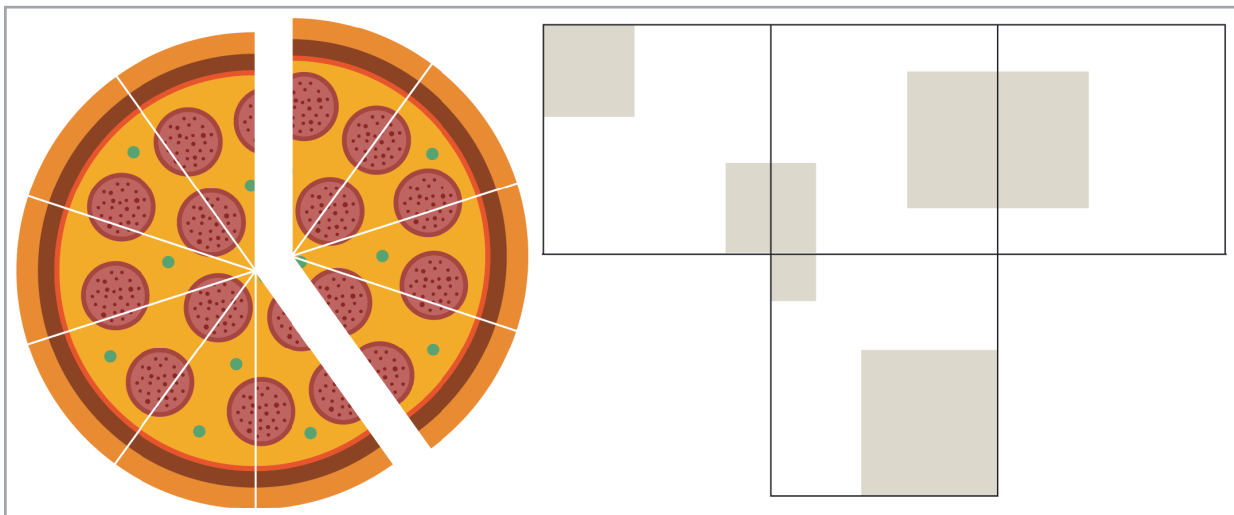
A The Scalp Hair Assessment PRO™: assessment of terminal scalp hair loss at the time of completion using five severity categories that include descriptors and percentages from 'No missing hair (0% missing; full head of hair)' to 'Nearly all or all (95–100% missing hair)'

- Three versions were tested: (i) without percentages, (ii) with spaces for patients to provide percentages for each severity category and (iii) final version with percentages
- B PRO Measure for Eyebrows™: four-point assessment of gaps or thinning of eyebrow hair at the time of completion from 'full eyebrows' to 'no or barely any eyebrow hairs'
- C PRO Measure for Eyelashes™: four-point assessment of gaps in eyelash hair at the time of completion from 'full eyelashes' to 'no or barely any eyelash hair'
- D PRO Measure for Nail Appearance™: four-point assessment of severity of fingernail and toenail damage (pitted, rough, brittle, split) at the time of completion from 'not at all damaged' to 'very damaged'
- E PRO Measure for Eye Irritation™: four-point assessment of severity of eye irritation (itching, stinging, burning, dry) in the past 7 days from 'not irritated' to 'severely irritated'

Exploration of whether categories 0 or 1 were acceptable thresholds for clinically meaningful treatment success was investigated for each measure by asking patients about the amount of change needed to make them happy. Patients also reviewed accompanying photoguides<sup>29</sup> for the eyebrow, eyelash and nail appearance PRO measures, which contain images of two to three patients edited to show different levels of hair loss/nail damage corresponding to each severity category.

## Sampling strategy

Eligible patients (see Table 1) were recruited by clinicians at University of California Irvine, Dawes Fretzin Clinical Research Group, Northwest Dermatology and Research Center and Yale University. Purposive sampling aimed to recruit a clinically and demographically diverse population, in particular to inform understanding of age differences among adolescents with AA (Table 1). A sample size of up to 12 participants was



**Figure 1** Images used for the percentage tasks. Left: What percentage of a 10-slice pizza is missing after four slices have been taken away? Correct answer 40%. Right: What percentage of the T-shape is not coloured in? The T-shape graphic was chosen as an abstract representation of the scalp with the left and right arms representing the left and right sides of the scalp, the centre block representing the top of the scalp and the bottom stem representing the back of the scalp. Correct answer 70%.

Table 1 Sample eligibility and diversity criteria

Inclusion criteria		
1 Male or female		
2 Aged 12–17 years at the time of consent		
3 AA diagnosed by a clinician and determined by:		
a) Patient currently has at least 50% scalp involvement (SALT score $\geq$ 50) and	OR	c) Patient has previously had at least 50% scalp involvement (SALT score $\geq$ 50) at any prior timepoint
b) Patient has a history of AA episode (stable or worsening) lasting >6 months but <8 years		
4 Patient and parent/legal guardian is able to read, understand and give written informed consent		
5 Patient speaks English fluently and can read and write US-English		
6 In the opinion of their physician, the patient has the physical, cognitive, reading and linguistic capacities sufficient to allow her/him to actively participate in a 90-min interview		
Exclusion criteria		
1 Patient has a diagnosis of active psoriasis, atopic dermatitis or other dermatological condition that in the opinion of the physician may be severe enough to impact the results of this study		
2 Patient has any other serious condition which may interfere with study participation or results		
3 Patients with other forms of alopecia		
4 Patient or their parent/guardian is a known substance abuser		
Sample diversity criteria (target quota)		
• Currently has $\geq$ 50% scalp hair loss (minimum $n = 5$ )		
• Aged 12–14 years (minimum $n = 3$ )		
• Nonwhite (minimum $n = 3$ )		
• Patients with eyebrow and/or eyelash involvement (no specific target)		
• Male and female (no specific target)		
AA, alopecia areata; SALT, Severity of Alopecia Tool The SALT <sup>8</sup> is an instrument for determining the extent of scalp hair loss in AA, based on the percentage of exposed scalp surface area on the top, back and each side of the scalp scored from 0 (absence of hair loss) to 100 (complete hair loss)		

sought based on consideration of the ISPOR taskforce guidance for establishing content validity of PRO measures,<sup>31,37</sup> recruitment feasibility assessment conducted prior to study initiation and experience from previous AA studies.<sup>9,10,28,29,33</sup>

### Ethical review

The study protocol was approved by the Western Institutional Review Board (ref. 20191772). Written informed assent/consent was obtained from each adolescent with AA and their parent/guardian prior to interview participation. Patients received a gift card for their time.

### Analysis

Interview transcripts underwent a two-step analysis process: (i) review and deductive, semantic coding<sup>38,39</sup> in ATLAS.ti v7.5, qualitative analysis software, based on the patient interview guide and analysts' perceptions; (ii) individuals analysed themes using an experiential, realist thematic approach for concept elicitation data<sup>38,39</sup> and framework<sup>40</sup> analysis techniques for cognitive interview data. IDs were assigned to protect participants' identities in the following format: number assigned in order of interview scheduling (01–11) – clinician-

reported percentage of missing scalp hair/SALT<sup>8</sup> score (0–100%) – sex (M, male; F, female).

Clinical, demographic, treatment success and percentage task data were analysed using descriptive statistics (e.g. mean, standard deviation).

### Researcher characteristics/reflexivity

The primary researchers who designed the study and conducted and analysed the interviews (J.M., H.K. and N.V.J.A.) were involved in the initial development of the PRO measures.<sup>28,29</sup> This experience enabled careful design of the study interview guide to ensure that questions were nonleading and awareness of pre-existing assumptions to mitigate confirmation biases during interpretation of data. The interviewers did not have any existing relationship with the participants.

## Results

### Sample

Eleven adolescents with AA with  $\geq$  50% scalp hair loss (presently or in the past) participated (Table 2; a 12th enrolled patient withdrew from the study because of family

**Table 2** Clinical and demographic characteristics (n = 11)

Characteristic	n (%) or mean (SD; range)
Scalp hair loss, n (%)	
Currently has $\geq$ 50% scalp hair loss	9 (82)
Previously had $\geq$ 50% scalp hair loss <sup>a</sup>	2 (18)
Eyebrow loss, n (%)	
Current	9 (82)
Previous	1 (9)
Never	1 (9)
Eyelash loss, n (%)	
Current	9 (82)
Previous	1 (9)
Never	1 (9)
Nail involvement, n (%)	
Current	4 (36)
Previous	2 (18)
Never	5 (45)
Years since AA diagnosis, mean (SD; range)	5.9 (4.0; 1.1–12.8)
SALT score/current % of scalp hair loss, mean (SD; range) <sup>b</sup>	69.6 (38.3; 0.0–100.0)
Patients with $\geq$ 95% scalp hair loss	4 (37)
Current treatment for AA, n (%)	5 (45)
Topical steroid/clobetasol	2 (18)
Dupilumab (Dupixent)	1 (9)
Iron + vitamin D	1 (9)
Minoxidil (Rogaine)	1 (9)
Steroid injection	1 (9)
Tofacitinib (Xeljanz 5 mg)	1 (9)
JAKi experienced or naïve, n (%)	
Currently receiving JAKi	2 (18)
Previously received JAKi	1 (9)
Naïve	5 (45)
Unknown, participating in blinded clinical trial (JAKi or placebo)	3 (27)
Months since enrolment in clinical trial, mean (SD; range)	5.7 (4.0; 2.0–10.0)
Concomitant illnesses, n (%)	9 (82)
Atopic rhinitis	7 (64)
Atopic dermatitis	4 (36)
Asthma	2 (18)
Thyroid disease	2 (18)
Acne	1 (9)
Anxiety	1 (9)
Depression	1 (9)
Heart disease	1 (9)
Vitiligo	1 (9)
Age (years), mean (SD; range)	15 (1.5; 12.0–17.0)
Sex, n (%)	
Male	5 (45)
Female	6 (55)
School grade, n (%)	
7th	1 (9)
8th	1 (9)
9th	3 (27)
10th	1 (9)
11th	5 (45)

(continued)

**Table 2** (continued)

Characteristic	n (%) or mean (SD; range)
Race/ethnicity, n (%)	
White	6 (55)
Black or African-American	2 (18)
Hispanic	2 (18)
Other, mixed, multi-ethnicity: Russian/Indian	1 (9)

AA, alopecia areata; JAKi, Janus kinase inhibitor; SALT, severity of alopecia tool. <sup>a</sup>Two participants previously had  $\geq$  50% scalp hair loss for 5.0 months and 3.3 years, respectively, prior to their interview. <sup>b</sup>SALT score used where site used the SALT (n = 10) or general clinician assessment of percentage of scalp hair loss used where site did not use SALT (n = 1).

commitments). Parents of four participants were present during their interview but did not contribute to the interview. Based on good understanding of the PRO measures demonstrated across the sample, further interviews were not considered necessary to determine whether the measures and accompanying photoguides were fit-for-purpose in an adolescent population.

Adolescent participants [mean age 15.0 (SD 1.5) years] had been diagnosed with AA for a mean 5.9 (SD 4.0) years and had a mean 69.6% (SD 38.3%) scalp hair loss. Almost all had current eyebrow loss (n = 9; 82%) and/or eyelash loss (n = 9, 82%), about a third had current nail involvement (n = 4; 36%) and almost half (n = 5, 45%) were receiving treatment for their AA at the time of interview. Five (45%) adolescents had never received Janus kinase inhibitors (JAKi), three (27%) were enrolled in a blinded JAKi clinical trial. Diversity in terms of sex (n = 6 females; 55%) and ethnicity (n = 5 non-white; 45%) was achieved.

## Concept elicitation

### Signs/symptoms and impacts

Adolescents reported multiple current/previous AA signs/symptoms, which they described in different ways (Table 3). Descriptions of scalp hair/hair loss mostly involved location and patches. Eyebrow and eyelash hair/hair loss were described in terms of amount/quantity.

Scalp hair loss was the most bothersome sign/symptom of AA for the majority of adolescents and many reported eyebrow and eyelash hair loss among their top three most bothersome signs/symptoms (Table 4). Overall, more female (n = 6) than male (n = 1) participants rated their scalp hair loss as most bothersome because it was the most obvious area of hair loss to others or took the most work to cover up (especially compared with eyebrows, which were easier to hide). Three male participants considered eyebrow loss to be more bothersome than their scalp hair loss because they felt they

Table 3 Adolescents' descriptions of current/previous signs

Sign	Concepts/attributes described	Supporting quotes
Scalp hair (n = 11) <sup>a</sup>	Location, patches, thickness, amount, colour, length, whether it was straight or curly, quality	<b>10-67-F:</b> 'It is mostly in the front area that it's come back except for a little patch on the left side of my head.' <b>04-93-F:</b> 'It's growing in, I have different patches on my head like some are more than others, like little patches.' <b>08-2-M:</b> 'Out of like 100%, I'd say that [...] 45% of my hair was gone.' <b>07-100-M:</b> 'I mean there is like barely like a couple of hairs. So like not really much.'
Eyebrows (n = 10)	Amount (percentage, bald spots, patches), density (thin, peach fuzz), colour change (blonde)	<b>07-100-M:</b> 'Like for my eyebrows, they started out just small patches like falling out. And then maybe like a couple months ago they completely all fell out'
Eyelashes (n = 9)	Quantity, length, weak	<b>01-100-M:</b> 'My eyelashes. Ever since they fell out, they haven't started to come back or I haven't seen any hairs on them at all.' <b>03-60-F:</b> 'They're still there. It's just that there's not as much. [...] They're like short and not as full. [...] Like how some people like fake eyelashes, how there's like a lot of them, there's not as much on mine.'
Nails (n = 5) <sup>b</sup>	Indents/bumps/craters, lines/ridges, break easily/soft, scratched up/scrapes, curved up, longer to grow	<b>05-100-M:</b> 'They used to have the indents in them, the ridges, that would run down. My nails, they haven't really been affected other than that.'
Other areas <sup>c</sup>	Arms (n = 6), body hair (n = 4), chest hair (n = 2), entire body (n = 6), male facial hair (n = 2), legs (n = 4), underarms (n = 1)	<b>08-2-M:</b> 'Losing it, I mean, I didn't have a lot of arm hair to begin with, but when I lost it, I knew it. I knew I was going to lose all my hair at the end of the day, so I wasn't too surprised about it. That's for my arms at least, though. It wasn't that shocking.'

AA, alopecia areata <sup>a</sup>Concept/attribute descriptions provided by seven of 11 patients. <sup>b</sup>Two were unsure if their nail involvement was AA-related despite their doctor/dermatologist assessing their nails. <sup>c</sup>Two female participants commented that they did not mind their body hair loss because it meant that they did not have to shave and two male participants (both aged 14 years) were unsure whether they had AA-related hair loss in some areas of the body (chest, beard) because they had never seen hair in those areas.

would 'look weird' (05-100-M) if they had scalp hair without eyebrows; although, when asked, two said they would be interested in a treatment that improved their scalp hair only 'just because I'd want my hair back [...] some hair is better than no hair, so I would definitely take my head back' (08-2-M).

Although many (n = 9) of the adolescents showed resilience and some level of acceptance of their AA and all who were asked described mostly supportive/understanding friends (n = 10) and family (n = 8), emotional, psychological and functional impacts of visible hair loss were prominent. These impacts included worry (n = 9), insecurity/inadequacy/self-consciousness (n = 7), perceived or actual social judgement (n = 8), sadness (n = 7), difficulties at school (n = 8; one participant was mostly home-schooled), time spent disguising AA (n = 7) and limiting or avoiding hobbies/sporting activities (n = 7). Various individual sensations or physical impacts of scalp hair loss (e.g. sensitivity, dryness, itching, sunburn, poor thermoregulation) were reported (n = 7) but bothered only one participant (Table 4). Eye irritation (n = 6) was described using terms such as burning, stinging, itchiness, soreness and wateriness. Eye irritation was attributed to eyebrow and/or eyelash loss causing sweat, debris and/or glare/light getting into the eyes and was experienced intermittently, to varying degrees of severity and affected some participants' ability/desire to do sports. Table S2 (see Supporting Information) shows a full list of impacts and supportive quotes.

### Amount of scalp hair and use of percentages

Eight adolescents spontaneously described (n = 3) or were asked to describe (n = 5) the amount of hair they had on their head, either at the time of the interview and/or during a previous stage of their AA. Patients described their current/previous amount of scalp hair qualitatively (n = 5) and/or as a percentage/fraction (n = 4). When asked directly about the use of percentages, one other participant said that they had thought about the amount of hair on their head as a percentage (total five). Six participants had not thought about their amount of scalp hair as a percentage, with some explaining that they just thought about whether there was 'a lot or a little' (03-60-F) or that they didn't think about the amount at all.

### Understanding of percentages

Results of the structured tasks used to gauge how well participants understood percentages are presented in Table 5. All adolescents showed some level of understanding of percentages. Ten (91%) successfully completed at least two of the percentage definition, pizza and T-shape tasks; although two of these participants incorrectly overestimated the total amount of scalp hair they had by 30% more than their clinician's assessment. One participant gave incorrect responses to the percentage definition, pizza and T-shape tasks, but correctly

Table 4 Top three most bothersome signs/symptoms

Sign/symptom	Ranking, n (%)			Supporting quotes
	1 (n = 11)	2 (n = 10)	3 (n = 7)	
Scalp hair loss	7 (64)	3 (30)	0 (0)	<b>02-50-F:</b> 'Scalp, eyebrows, eyelashes. [...] Scalp first] because I have to do the most for it by wearing the wig every day and it makes the biggest difference.'
Eyebrow hair loss	3 (27)	6 (60)	0 (0)	<b>12-92-8-M:</b> 'Eyebrows is serious because like if I didn't have hair on my scalp but I had eyebrows then it wouldn't look so bad. [...] it would just look like I'm a normal kid that like doesn't have hair on their scalp.'
Eyelash hair loss	1 (9)	0 (0)	6 (86)	<b>01-100-M:</b> 'The most annoying probably would be around the eyes [...] I: that's your eyebrows or eyelashes? Eyelashes.'
Leg hair	0 (0)	0 (0)	1 (14)	<b>08-2-M:</b> 'The third, legs, I feel like this is more just me being weird, but I always liked my legs to look really manly. I don't know why, but when I play lacrosse, I think it's just saying when you look at someone's legs and they have hairy, manly legs, I think, "Oh, he's probably good," but that could just be in my head. I don't know.'
Physical irritation on scalp	0 (0)	1 (10)	0 (0)	<b>01-100-M:</b> 'I've noticed that whenever chlorine touches my skin which I think if it has empty hair follicles so that's basically the small places where chlorine can get into, it always made my head feel weird and even when I take a shower, it just gets – after that shower just like evaporates itself and gets really dry. [...] It just feels a little bit tighter and the skin doesn't really move as much and it just doesn't feel the greatest.'

estimated her current amount of hair (about 6% less than her clinician-rated SALT score). No relationship between participant age and ability to define or use percentages was identified.

### Scalp treatment success

Participants were asked if there was an amount of hair coverage, less than 100%, that would make them happy after taking an 'imaginary' treatment. Participants considered a median 80% scalp hair coverage (range 50–95%) to be clinically meaningful and indicative of treatment success, after 9–12 months of treatment (Figure 2). When asked about other factors that were

important when considering if treatment had been a success, 10 participants described that the location of hair was important to some degree so that patches of missing hair could be covered (e.g. missing hair at the front of the head would be difficult to cover). Other factors affecting treatment success included hair length (n = 2), quality (n = 1) and thickness (n = 1).

### Cognitive debriefing

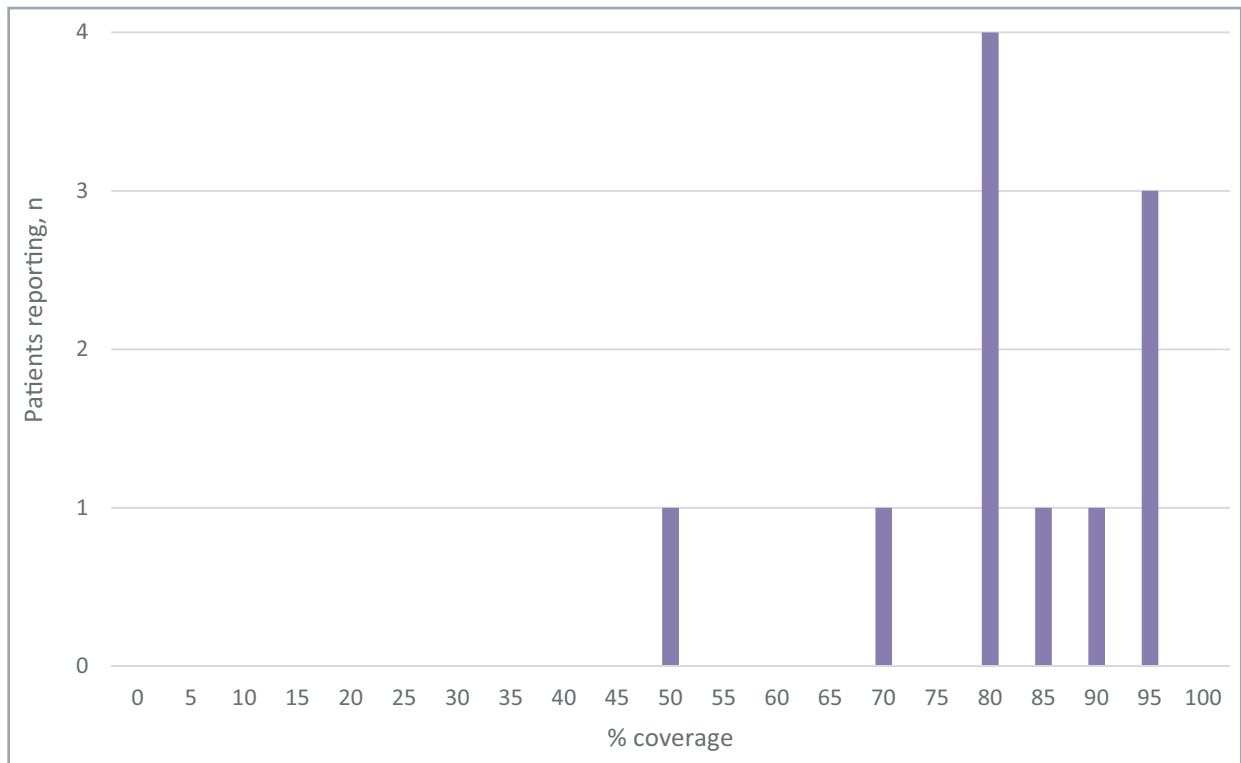
#### Scalp Hair Assessment PRO™

Overall, all 11 adolescents could provide a response to the Scalp Hair Assessment PRO™ and understood the measure's

Table 5 Results of the structured percentage understanding tasks

Task	Correct, n (%)	Answers
Define percentage (n = 11)	8 (73) <sup>a</sup>	Participants clearly demonstrated that they understood percentages represented a proportion of a whole: 'A percentage is a fraction, but a different way to say a fraction. So it's the same thing but a fraction is a piece of something. A percentage is a piece of a whole.' (10-67-F)
Percentage of pizza taken away; correct answer 40% (n = 11)	9 (82) <sup>b</sup>	Mean 39% (SD 14%) Median 40% (range 4–65%)
Percentage of T-shape not coloured in; correct answer 70% (n = 11)	9 (82) <sup>c</sup>	Mean 66% (SD 17%) Median 70% (range 20–85%)
Difference between participant estimation and clinician assessment of hair loss (n = 10)	8 (80) <sup>d</sup>	Mean 9% (SD 13%) Median 5% (range 0–33%)

<sup>a</sup>Three participants unable to provide a definition were aged 12, 14 and 16 years. <sup>b</sup>Two incorrect answers were '10% or 4%' and '65%', by participants aged 16 and 17 years. <sup>c</sup>Within an arbitrary allowance of  $\pm 10\%$ , two incorrect answers were 85% and 20%, both aged 16 years; median of ranges provided by two participants was used to calculate the sample mean and median. <sup>d</sup>Within an arbitrary allowance of  $\pm 10\%$ , two responses were 32% and 33% lower than clinician assessment (i.e. participants thought they had a considerable amount more hair than clinician assessment), both aged 14 years; the score was reversed for five participants who estimated percentage of hair coverage; the median of ranges provided by two participants was used to calculate the sample mean and median.



**Figure 2** Amount of scalp hair coverage that would make participants happy after 9–12 months of treatment ( $n = 11$ ). One participant gave the response of ‘Almost 100%’, which for analysis purposes, and to be conservative, has been extracted as 95%, the next 5% decrement below 100%.

instructions were to assess missing hair as opposed to hair coverage. All 11 participants correctly considered areas of vellus hair as missing hair; two participants commented that the definition of ‘vellus hair’ in the measure’s instructions helped them answer the question (all understood ‘peach fuzz’ or ‘baby hair’).

Participants first reviewed a version of the PRO measure without percentages included in the response options. Participants were largely consistent in their understanding of the response category wording, and some spontaneously used percentages or proportions to describe the differences between each category. When asked, all 11 participants could provide percentages of missing hair for each severity category, although the ranges provided varied (Figure 3). Seven participants found this task easy. Three who expressed some confusion and/or difficulty initially wrote percentages for hair coverage, which may have been related to discussion of hair coverage earlier in the interview, and understood their mistake when the task was re-explained.

When shown the final version of the Scalp Hair Assessment PRO™, participants were told that the included percentage ranges of missing hair were decided with input from doctors who treat people with AA and input from adults who have AA. All 11 participants stated that the final percentages could be used as presented, although five suggested alternative percentage ranges.

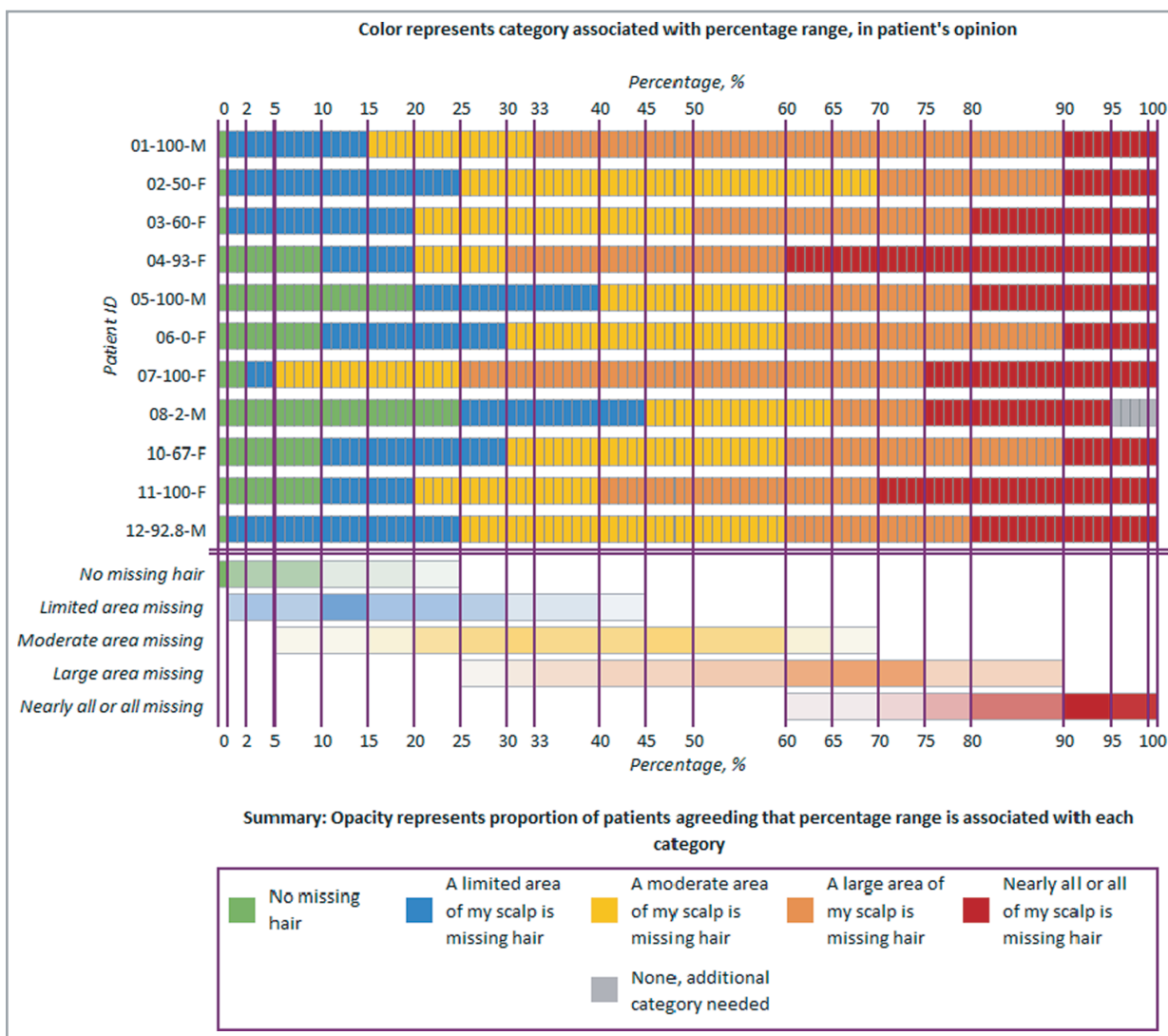
Overall, most (seven of 10) participants asked said they preferred the version of the measure with percentages, as percentages helped avoid any confusion or subjective interpretation of the response option wording. Participants (three of 10) who did not feel comfortable using percentages could still complete the measure using the descriptors.

Participants considered themselves to be accurate raters of their scalp hair loss, although most felt that both they and their doctor should make ratings. Nine participants considered reaching category ‘1 Limited area (1–20% missing hair)’ after 9–12 months would indicate successful treatment. Two participants felt they could not be satisfied until they had a full head of hair with no areas of loss.

#### PRO Measure for Eyebrows™, PRO Measure for Eyelashes™, PRO Measure for Nail Appearance™ and accompanying photoguides

All 11 adolescents could understand and provide a response to the PRO Measure for Eyebrows™, PRO Measure for Eyelashes™ and PRO Measure for Nail Appearance™. Any reported problems or suggested changes (e.g. confusion around rating ‘gaps’ and/or ‘thinning’ in the eyebrow measure, assessing upper and lower eyelashes) were minor and did not prevent any participants from making an assessment. Moreover, participants thought that the eyebrow (all 11), eyelash (nine of 10)





**Figure 3** Percentage ranges suggested by participants to represent each severity category of the Scalp Hair Assessment PRO™. For this task, participants completed a version of the Scalp Hair Assessment PRO™ with spaces to provide percentages for each severity category: Use mirrors to look at your entire scalp. Please rate the total area of your scalp that is missing hair right now. Areas of vellus hair (peach fuzz or baby hair) should also be considered as missing hair. Please select one answer. No missing hair (I have a full head of hair) \_\_\_\_%. A limited area of my scalp is missing hair \_\_\_\_%. A moderate area of my scalp is missing hair \_\_\_\_%. A large area of my scalp is missing hair \_\_\_\_%. Nearly all or all of my scalp is missing hair \_\_\_\_%.

and nail (10 of 10) photoguides would be helpful when answering the measures (including two of three patients who did not fully agree with individual photos included in the eyelash photoguide). In particular, the photoguide for the PRO Measure for Nail Appearance™ helped some participants who did not understand nail damage descriptors ('pitted' and/or 'brittle') included in the measure.

For each of these signs/symptoms, participants were comfortable rating themselves but generally felt that obtaining a doctor's rating would be important during a clinical trial and that the doctor would be the most informed and accurate rater compared with them or their parents. In terms of treatment success, ultimately the majority of participants said they would be happy to reach at least category '1 Minimal hair

loss/a little damage' on the eyebrow (all 11), eyelash (nine of 10) and nail (seven of eight) measures after 9–12 months of treatment, although most would prefer/need to reach category '0' (eight of 11, seven of 10 and six of eight, respectively).

**PRO Measure for Eye Irritation™**

All 10 participants who reviewed the PRO Measure for Eye Irritation™ generally understood and could complete the measure. Half (three of six) of the participants would consider reaching category '1 A little irritated' successful after 9–12 months of treatment and half needed their eyes to be '0 Not irritated' following treatment.

## Discussion

The content validity of the Scalp Hair Assessment PRO™, PRO Measure for Eyebrows™, PRO Measure for Eyelashes™, PRO Measure for Nail Appearance™ and PRO Measure for Eye Irritation™ was initially established in line with FDA<sup>26,30</sup> and industry<sup>31,32,34</sup> PRO guidance with dermatologists and adult patients from North America.<sup>10,28,29</sup> Demonstration of content validity in one population (US adults) cannot be assumed to apply to other groups. To this end, the content validity of the measures have been explored with dermatologists and adult patients in Japan<sup>36</sup> and, in this study, with adolescent patients aged 12–17 years. These qualitative interviews with 11 adolescents with experience of ≥ 50% AA-related scalp hair loss used novel and innovative methods to not only provide evidence for the content validity of these measures and accompanying photoguides in an adolescent population but also to support findings of the previous dermatologist and adult patient interview studies.<sup>9,10,28,29,36</sup>

Adolescents' descriptions of their AA signs/symptoms during the concept elicitation portion of the interview supported each PRO's measurement concepts. Scalp hair loss was the most bothersome sign/symptom, followed by eyebrow and eyelash hair loss. Although location of scalp hair loss/regrowth was important, the amount of hair appeared to be more critical. Additionally, participants mostly described their eyebrows/eyelashes in terms of amount, and used descriptions of nail damage and eye irritation that corresponded to example descriptors included in the PRO measures (e.g. 'indents' corresponding to pitted nails and 'burning' eye irritation). Innovative structured tasks, not typically used in clinical outcomes assessment development, were designed to gauge adolescents' ability to use percentages because percentages are included in response options of the Scalp Hair Assessment PRO™. The tasks were developed after reviewing tasks used with schoolchildren of a similar age in the UK (Key Stage 3/4) as a 'real world' way of testing comfort/understanding with percentages. During these structured tasks, a good level of understanding of percentages was demonstrated across the entire age range of the sample.

The adolescents showed good understanding of the PRO measures during cognitive interviews and were able to use the measures to rate their signs/symptoms.<sup>35</sup> Most participants supported the inclusion of percentages of hair loss in the Scalp Hair Assessment PRO™ (e.g. '50–94% missing hair'); a few who were not comfortable using percentages confirmed that they could complete the measure using the corresponding descriptors (e.g. 'a moderate area of missing hair'). Additionally, the photoguides for the PRO Measure for Eyebrows™, PRO Measure for Eyelashes™ and PRO Measure for Nail Appearance™ were reported to be helpful visual aids to facilitate ratings and their use alongside the measures is recommended. These single-item measures are expected to have minimal completion burden. Although the adolescents felt that they should self-report these signs/symptoms, doctors' ratings were considered important to obtain because of clinical experience and expertise.

It is important to define responders in clinical trials to evaluate treatment success, and additionally important that patients should inform what a 'responder' is.<sup>41,42</sup> Responder definitions of treatment success reported by adolescents in this study supported those established with dermatologists and adult patients in North America and Japan.<sup>28,36</sup> Defining SALT score ≤ 20 (i.e. 0–20% scalp hair loss) as clinically meaningful treatment success was supported by participants, who mostly confirmed they would consider a treatment successful if they achieved a median 80% scalp hair growth (i.e. 20% scalp hair missing). Additionally, participants reported that they would be happy reaching categories corresponding to no/minimal eyebrow loss, no/minimal eyelash loss, no/a little nail damage and no/a little eye irritation (categories 0 or 1) on the respective PRO measures following treatment. Patients' rating of scalp hair loss as the most bothersome AA sign/symptom suggested that recovery of scalp hair should be the primary endpoint in clinical trials for novel AA therapies.

The health-related quality of life impacts reported by adolescents in this study support many of those reported by adolescents elsewhere.<sup>18,24,25</sup> The adolescent experience of AA appears to be similar to that of adults;<sup>9,15,17,19,21</sup> however, a more in-depth study on the patient burden of AA in adolescents is needed. Although patients may cope with and become accepting of their AA, emotional, functional, psychological and psychosocial impacts remain. These impacts are primarily related to areas of hair loss visible to others, for example worry or insecurity/self-consciousness about perceived or actual judgement from others, which resulted in participants trying to conceal their AA or avoid situations that risked exposure.

Compared with a conceptual model of the experience of AA that this study's authors previously developed from interviews with 40 adults and five adolescents with AA,<sup>9</sup> 27 of 37 sign/symptom and impact concepts included in the model arose in this study. Differences may be explained by this study prioritizing exploration of the PRO measure signs/symptoms (e.g. nasal hair loss/irritation, dry/flaky and oily scalp skin, burning/inflammation sensations, nail pain were not probed) over exploration of impacts. However, seven concepts that did not arise in this study were not reported by adolescents in the previous study and therefore may not be relevant to the adolescent experience of AA (e.g. financial strain, guilt, impact on romantic/family relationships).

Limitations of this study are acknowledged. This study was completed in the US only and, as a result, may not be generalizable to other countries and cultures. Due to the small sample involved in this study, there was no attempt to prospectively analyse the data or draw conclusions by subgroups of age or sex. Three included participants were enrolled in a clinical trial and may have been exposed to similar PRO measures. Additionally, some participants' hair loss was assessed by a dermatologist just prior to their interview, which may have influenced their estimation/perception of hair loss. However, the descriptions provided and ability to

use percentages appeared broadly consistent across the sample and no age-related differences in understanding of the PRO measures or percentages were apparent. Additionally, the findings were generally supportive of similar interviews conducted previously with adults with severe AA.<sup>9,10,29,33</sup> Although this study supports the content validity of the suite of AA PRO measures in adolescents with severe AA, quantitative research to provide evidence of each measure's psychometric properties (e.g. reliability, ability to detect change)<sup>30</sup> is not yet completed.

This and other studies have demonstrated that hair loss is psychosocially burdensome to patients and time-consuming and difficult to hide.<sup>9,16–22</sup> Patients have demonstrated proficiency in assessing their own hair loss and informed that near-complete scalp hair regrowth ( $\leq 20\%$  missing hair/SALT score  $\leq 20$ ) would restore a sense of normality.<sup>28,33,36</sup> Therefore, it is not only feasible but critically important to assess the clinical signs of AA, including scalp hair loss, from the patient perspective.<sup>19,26,30</sup>

In conclusion, the Scalp Hair Assessment PRO™, PRO Measure for Eyebrows™, PRO Measure for Eyelashes™, PRO Measure for Nail Appearance™ and PRO Measure for Eye Irritation™ and accompanying photoguides are fit-for-purpose assessments of important AA signs/symptoms and, subject to further psychometric evaluation, can be used by adolescents with AA aged 12–17 years in clinical trials and clinical practice.

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## Data availability statement

The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality of the information. However, the corresponding author can be contacted for any data related questions.

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## Supporting Information

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

**Table S1** Example questions from the study interview guide.

**Table S2** Emotional, psychological, functional and physical impacts reported by adolescents.