BMJ Open

Patient preferences for atopic dermatitis medications in the UK, France and Spain: a discrete choice experiment

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To cite: Thomas C, Raibouaa A, Wollenberg A, *et al*. Patient preferences for atopic dermatitis medications in the UK, France and Spain: a discrete choice experiment. *BMJ Open* 2022;**12**:e058799. doi:10.1136/bmjopen-2021-058799

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058799).

Received 19 November 2021
Accepted 04 July 2022

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ABSTRACT

Objectives We aimed to quantify patient preferences for efficacy, safety and convenience features of atopic dermatitis (AD) treatments.

Design and setting Online discrete choice experiment survey.

Participants Adults in the UK, France and Spain who had used AD treatments during the past 2 years.

Primary and secondary outcome measures Preferences for attributes were analysed using a multinomial logit model. Willingness to make trade-offs was expressed as the maximum acceptable decrease (MAD) in the probability of achieving clear/almost clear skin at week 16.

Results The survey was completed by 404 patients (44.1±12.0 years; 65% women; 64% moderate/severe eczema). Most patients (68%) had no prior experience of using self-injectable treatments for AD or any other illness. Participants most valued increasing the chance of achieving a meaningful reduction in itch at week 16 from 20% to 50%, followed by reducing the risks of serious infections from 6% to 0% and of eye inflammation from 20% to 0%. Participants were willing to accept a decrease in the possibility of achieving clear/almost clear skin to obtain a treatment that can be paused (MAD=24.1%), requires occasional check-ups (MAD=16.1%) or no check-ups (MAD=20.9%) over frequent check-ups, is administered as a one time per day or two times per day oral pill versus a subcutaneous injection every 2 weeks (MAD=16.6%), has a 2-day over 2-week onset of action (MAD=11.3%), and can be used for flare management (MAD=5.8%).

Conclusions Although patients with AD most valued treatment benefits and risks, they were willing to tolerate reduced efficacy to obtain a rapid onset, oral administration, less frequent monitoring and a treatment that can be paused. Understanding patients' preferences for AD therapies, including new targeted therapies, can aid shared decision-making between clinicians and patients and support health technology assessments.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a discrete choice experiment, which allowed us to quantitatively assess the trade-offs that patients with atopic dermatitis (AD) are willing to make between clinical and non-clinical treatment characteristics.
⇒ Pilot testing and validity measures were performed to ensure that the target population could understand the survey and traded-off appropriately between the treatment attributes.
⇒ Study participants had predominantly self-reported moderate-to-severe AD (assessed with the Patient Oriented Eczema Measure), and these findings may not apply to the wider AD adult population, including those with mild or very severe AD.

INTRODUCTION

Atopic dermatitis (AD) is mostly treated using emollients and moisturisers, topical corticosteroids and calcineurin inhibitors, and, for severe cases, systemic immunosuppressants.[1 2] However, emollients and moisturisers may not be sufficiently effective, and conventional systemic immunosuppressants have many potential side effects and are not generally recommended for long-term maintenance of AD.[3 4] New targeted therapies for treating AD are now available. Dupilumab, a subcutaneously administered human monoclonal antibody inhibiting interleukin-4 and interleukin-13 signalling, was licenced in the USA and the European Union in 2017 for the treatment of AD.[5] Baricitinib and upadacitinib, oral small-molecule inhibitors of Janus kinases, were recently licenced in the European Union for the treatment of moderate-to-severe AD in patients who are candidates for systemic therapy.[6 7]

Several additional targeted therapies are in development, including a variety of monoclonal antibodies inhibiting interleukin signalling.[1 2 8] These new targeted therapies have different efficacy, risks and non-clinical attributes, especially the mode of administration. In other chronic diseases, some patients prefer oral over parenteral treatment because they perceive some barriers to parenteral administration, which may lead to reduced adherence.[9–11] Because non-health benefits cannot be captured in traditional

cost-effectiveness analysis, understanding to what extent they are valued by patients can help guide health technology assessment discussions[12–16] and inform shared decision-making at the point-of-care.[17]

Preferences for different treatment attributes, such as their benefits, risks, mode of administration and convenience features, can be elicited from patients using discrete choice experiments (DCEs).[18] In DCEs, participants are presented with a series of tasks where they have to select between different hypothetical treatment options, each of which is composed of one level from each attribute in such a way that they are forced to make trade-offs, such as a higher risk of an adverse event but improved efficacy. DCEs have the advantage that the results can be used to quantify to what extent participants value each of the different attributes and estimate the trade-offs they would be willing to make. We hypothesised that patients with AD would not value all attributes relevant for their treatment choices equally. In the current study, we used a DCE to elicit the preferences of patients for key efficacy, safety and convenience attributes of targeted AD therapies and examine the trade-offs they are willing to make between them.

MATERIALS AND METHODS

An online DCE survey was conducted between October and December 2019 in adults with AD living in the UK, France or Spain. In the DCE survey, participants completed a series of choice tasks in which they selected between hypothetical treatment options described by a set of attributes with different levels. Treatment attributes and levels included in the DCE were identified through a targeted literature review of Embase and MEDLINE for quantitative and qualitative preference studies and a review of product labels for AD treatments (search conducted 10 September 2018; see online supplemental methods and table 1 for details). The attribute levels included in the DCE (eg, likelihood of achieving clear or almost clear skin at week 16) were informed by clinical data from product labels for AD treatments (where available), including both baricitinib and dupilumab, reflecting the range of potential experiences that patients may have.[19 20] Attributes included the following: chance of achieving clear or almost clear skin at week 16, chance of achieving a meaningful reduction in itch at week 16, risk of eye inflammation, risk of serious infections, administration, flare management, long-term disease management, monitoring and speed of onset (table 1). In order to reduce the cognitive burden of the survey, we grouped attributes as benefits, risks and other. Prior research has found that grouping benefits and risks, and randomising the order of the groups and attributes within the groups, reduces the cognitive burden on participants, thereby reducing ordering effects and increasing choice certainty and the precision of preference estimates.[21]

Cognitive pilot interviews

To ensure the feasibility and robustness of the DCE, cognitive pilot interviews were conducted in the UK, France and Spain (n=5 per country). The interviews involved a total of 15 patients, who were recruited using the same eligibility criteria as the main study. Patients were recruited through a number of routes, including health care provider referrals, social media and patient databases. The interviews examined whether the chosen attributes and levels were relevant, tradeable and understandable to participants.[22] In addition, the cognitive pilot interviews assessed the complexity and clarity of the overall questionnaire. Each interview lasted approximately 60 min. Participants were provided a description of the study and completed the initial version of the study survey instrument online while sharing their screen with an interviewer and thinking aloud about the rationale behind their choices. While participants completed the DCE, interviewers probed them using a semi-structured discussion guide. At the end of the interview moderators assessed whether all attributes had been considered, and the overall relevance and plausibility of attributes and levels included in the survey; these assessments were interviewer observed and based on the patients' rationale behind decision-making during the interview.

The cognitive pilot interviews were conducted in two waves, with roughly half the participants in each wave. Updates were made after wave 1 and the revised survey was subsequently tested in wave 2. The textual updates after wave 1 were largely minor wording updates to improve the understandability of the survey. However, the presentation of the task and the denominator of serious infections was updated to be consistent with the other risk attribute (eye inflammation). In wave 1, attributes were not initially grouped as benefits, risks and other. The visualisation of the DCE was adjusted after wave 1 as some participants were misinterpreting the benefit/risk of a treatment. The updated survey grouped and labelled the attributes by category (benefits, risks, other). In wave 2, participants did not have problems understanding the benefits and risks of treatments and found it easier to consider a wider range of attributes. Patients were also asked if they thought any attributes were missing that they would want to know about when selecting a treatment. No missing attributes were identified.

The online DCE survey was initially tested in 29–30 participants per country. Minor updates were made to the visual presentation of the survey. Recruitment targets were to include an additional 115 participants in the UK, 115 in Spain and 85 in France.

Participants

Participants were recruited via recruiter databases, social media, patient associations and online patient panels. Adults (≥18 years) living in the UK, France or Spain with a self-reported diagnosis of AD for ≥12 months were eligible if they had received a topical or systemic therapy for AD

Table 1 Treatment attributes and levels included in the main discrete choice experiment

Treatment attribute	Description of the treatment attribute presented to participants	Levels
Itch reduction	Eczema (atopic dermatitis) causes your skin to itch. Treatments for eczema (atopic dermatitis) increase the probability of achieving a meaningful reduction in itch severity.	**2 out of 10 (20%):** There is a 20% chance of achieving a meaningful reduction in itch severity (reference level). **4 out of 10 (40%):** There is a 40% chance of achieving a meaningful reduction in itch severity. **5 out of 10 (50%):** There is a 50% chance of achieving a meaningful reduction in itch severity.
Skin appearance	Eczema (atopic dermatitis) affects the way your skin looks due to flaking, redness, swelling, oozing, crusting, bleeding. Treatment for eczema (atopic dermatitis) may improve your skin condition, but different treatments have different impacts. In this survey, we will ask you to consider the chance of achieving clear skin after 16 weeks starting the treatment.	**1 out of 10 (10%):** After taking treatment for 16 weeks, there is a 10% chance you will have clear/almost-clear skin (reference level). **2 out of 10 (20%):** After taking treatment for 16 weeks, there is a 20% chance you will have clear/almost-clear skin. **4 out of 10 (40%):** After taking treatment for 16 weeks, there is a 40% chance you will have clear/almost-clear skin.
Eye inflammation	All treatments have some risk of negative side effects. Some treatments can cause minor eye infections. You may have swollen eyelids, feel sensitivity to light, feel itching or burning in your eyes or have pink discolouration of the white in your eyes. This can be treated but may require interruption to treatment. Other treatments do not increase your risk of getting an eye inflammation.	**0 out of 100 (0%):** Your treatment does not increase the chance of an eye inflammation. **10 out of 100 (10%):** There is a 10% chance of experiencing an eye inflammation. **20 out of 100 (20%):** There is a 20% chance of experiencing an eye inflammation (reference level).
Serious infections	All treatments have some risk of negative side effects. Some treatments reduce your immune system's effectiveness at fighting off illness and can result in serious infections, such as pneumonia or blood poisoning, that may require treatment and hospitalisation; you may be hospitalised for around 1 week. There is always a very low risk of serious infection and this low risk may be increased.	**0 out of 100 (0%):** Your treatment does not increase the risk of serious infection. **3 out of 100 (3%):** 3 out of 100 people will experience a serious infection. **6 out of 100 (6%):** 6 out of 100 people will experience a serious infection (reference level).
Speed of onset	All medications for eczema (atopic dermatitis) take some time to start working. Some medications will start to work in 2 days, but others can take 1 or 2 weeks.	**2 days:** Your medication will begin to work 2 days after starting the treatment. **1 week:** Your medication will begin to work 1 week after starting the treatment. **2 weeks:** Your medication will begin to work 2 weeks after starting the treatment (reference level).
Flare management	For some treatments, your doctor can increase your dose if your symptoms get worse (flare-ups). After the flare is controlled, reducing the dose again may also be an option. However, other treatments cannot be adjusted in this way and you will remain on a fixed dose, even if your symptoms change.	**Yes:** Your doctor can increase or decrease your dose when your eczema (atopic dermatitis) gets worse or improves. **No:** Your doctor cannot increase or decrease your dose when your eczema (atopic dermatitis) gets worse or improves (reference level).
Long-term disease management	Some treatments for eczema (atopic dermatitis) need to be used continuously, without the option to stop and restart therapy when you want. Interruption of treatment, also known as a treatment holiday, can lead to a loss of efficacy over time. This means the therapy may not work as well when you restart treatment. These treatments must be used continuously and cannot be paused. Other treatments can be stopped and restarted (treatment holiday), with no impact on how effective the treatment is. Some treatments should not be used for the long-term, as they can have life threatening side effects, if used for a long period of time.	**Yes, with the possibility for pauses:** Treatment can be taken long-term, and can be paused with no impact on how effective the treatment is. **Yes, without the possibility for pauses:** Treatment can be taken long-term, but must be taken continuously for there to be no impact on how effective the treatment is. **Should not be used long-term:** You can pause the treatment, but using for the long-term may result in life threatening side effects (reference level).

Continued

Table 1 Continued

Treatment attribute	Description of the treatment attribute presented to participants	Levels
Administration	Treatments are not all given/taken in the same way; for instance, some are pills, others are injections or topical creams. In this study we will only be considering pills and injections.	**Oral pill, one time or two times per day** **Injection under the skin, every 2 weeks:** This is a subcutaneous injection, below the skin, but above muscle, usually injected into the thigh/stomach area. You can administer the injection yourself or a healthcare professional can administer it. If you choose to administer it yourself, you may need to be trained by a nurse on the injection technique. Treatment is once every 2 weeks (reference level).
Check-ups	Some treatments require periodic blood tests taken by your doctor, because although you may not feel any symptoms, some eczema (atopic dermatitis) medications can have a negative impact on your body.	**Frequent check-ups required:** Blood tests every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable (reference level). **Occasional check-ups required:** Blood tests at beginning of treatment, after 12 weeks, and then routinely, as determined by your doctor, while on treatment. **No check-ups required.**

In each choice task, participants were asked to choose between different treatment options, each composed of one level from each of the attributes. Sensitivity of participants to changes in levels for each attribute were measured relative to the reference level, which is the level that patients least prefer. For example, the reference level for risks is the highest level and for efficacy the reference level is the lowest level.

in the past 2 years. Participants also had to be able to speak, read and write the official language of the respective country. Potential participants were excluded if they had a diagnosis of psoriasis, acne, lupus erythematosus, skin cancer or any other condition that could interfere with participation in and completion of the interview. To account for the possibility that preferences differ between participants with and without self-injectable experience, the study was initially designed to include a target of 40% of participants with prior self-injectable experience, although this was reduced to 30% during the study to allow enough participants to be recruited.

All participants provided online informed consent before participating. Participants in the cognitive pilot consented to being audio recorded. Participants were remunerated for completing the study.

DCE survey

The DCE was generated using Ngene software V.1.2.1 (ChoiceMetrics, Sydney, Australia) using a D-efficient design that was assessed against good experimental design properties. The design was optimised for the estimation of a multinomial logit (MNL) model, and, where appropriate, directional priors. The experimental design of the DCE included 36 experimental choice tasks split into three blocks, such that each participant would complete only 12 experimental choice tasks. Participants in the pilot interviews did not struggle with the number of attributes in the choice tasks. Full profiles (where no attributes were fixed to a set level to simplify the design) were therefore used. In each choice task, participants were asked to choose between two hypothetical treatment options (A and B) and an opt-out of staying with their 'old treatment', wherein each treatment option was composed of one level from each of the attributes (figure 1). If a participant selected the 'old treatment' option, they answered a follow-up question asking them to choose between treatment options A and B. We used a recommended status-quo opt-out option,[23] which remained fixed throughout the survey (while treatment A and B varied). For methodological reasons, to not overestimate patients' willingness to accept risks, the risk of adverse events was set to 0% for both eye inflammation and serious infections. Since this would not reflect patients varied current treatments, the opt-out option was referred to as 'old treatment'. The order of the 12 experimental choice tasks and of the attribute groups (benefits, risks, other) within the choice options was randomised across participants to minimise the influence of ordering effects.[24 25] In addition to the 12 experimental choice tasks, participants answered 2 choice tasks to assess internal validity.[26] Task 13 was a repeat of the third experimental choice task seen by the participant and was intended to check the stability of their choices. Task 14 was a dominated-choice test in which one treatment option was as good as or better than the other option for all attributes and was intended to test attendance to the tasks.

In addition to the DCE, participants completed a sociodemographic/clinical questionnaire, indicated their willingness (on a 5 point scale form not willing to very willing) to have a medication that required a subcutaneous injection for each dose, and completed the Set of Brief Screening Questions to assess health literacy[27] and

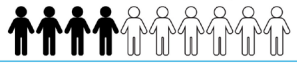
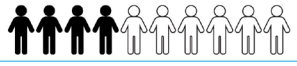
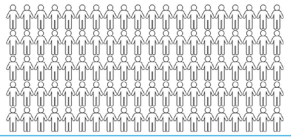
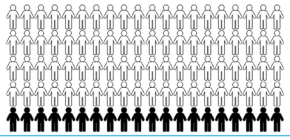
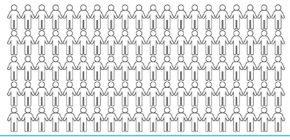
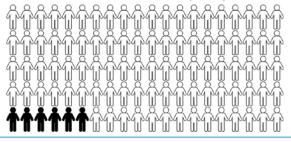
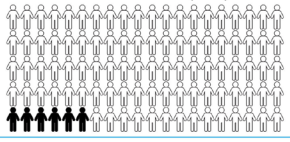
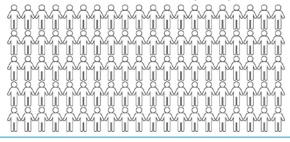
		Treatment A	Treatment B	Your old Treatment
Benefits	Itch Reduction	4 out of 10 (40%) 	4 out of 10 (40%) 	2 out of 10 (20%) 
	Skin Appearance	4 out of 10 (40%) 	4 out of 10 (40%) 	1 out of 10 (10%) 
Side Effects	Eye Inflammation	0 out of 100 (0%) 	20 out of 100 (20%) 	0 out of 100 (0%) 
	Serious Infections	6 out of 100 (6%) 	6 out of 100 (6%) 	0 out of 100 (0%) 
Other	Speed of Onset	1 week	2 weeks	2 weeks
	Flare Management	✓	✗	✓
	Long-term Disease Management	Yes, with the possibility of pauses	Yes, without the possibility of pauses	Should not be used long-term
	Administration	Oral pill  Once or twice daily	Injection under the skin  Every two weeks	Oral pill  Once or twice daily
	Check-ups	Occasional check-ups required	No check-ups required	Frequent check-ups required
	Choice	☐	☐	☐
	[*if old treatment is chosen*] Choice	☐	☐	

Figure 1 Example choice task.

five of the seven items from the Numeracy Scale to assess numeracy[28] to assess their ability to understand the attributes and levels presented and their engagement in the survey.

Validity assessments

For the dominance test, which presented one treatment option with higher levels of benefits and lower levels of risks, the number of patients selecting the superior (dominating) option as their preferred treatment was recorded; selecting the superior option indicated the survey sufficiently engaged participants. The number of patients selecting the same choices in the initial and repeated tasks was also recorded; selecting the same option in both questions indicated choice stability. A respondent was classified as a serial non-participant if they chose the same treatment option for all 12 experimental choice tasks. Decision-making was considered dominated when the respondent chose their preferred treatment option based on a single attribute in all 12 experimental choice tasks. For each choice task, response times in the lower 10% of the corresponding distribution were classified as fast and those in the upper 10% as slow. Attendance to the DCE survey was classified as inadequate if ≥80% of a participant's responses for the 12 experimental choice tasks were classified as too fast or too slow.

Statistical analysis

Statistical analysis was performed using R V.3.6.1 (R Foundation, Vienna, Austria). DCE preference data were analysed using a MNL model within the random utility maximisation framework[29] (see online supplemental methods for details). This model assumed that respondents chose the alternative that resulted in the highest utility (a measure of desirability) based on the included attributes and up to a random error.[30] The main results from this model were part-worth utility estimates, which reflect participants' sensitivities to changes in the treatment attributes. A dummy coding strategy was implemented to estimate preferences for discrete changes in the treatment attributes. In addition, the MNL model included two alternative-specific constants, one that

captured left–right bias (tendency to select the option presented on the left of the choice tasks) and one that captured a preference for the old treatment option.

A second MNL model with linearly coded attributes for the skin appearance attribute was also estimated to support the computation of the maximum acceptable decrease (MAD) in the probability of achieving clear or almost clear skin at week 16. The acceptability of the underlying hypothesis of linearity in preferences for changes in the skin appearance attribute was first verified (see online supplemental methods for details). The MAD analysis measured the percentage decrease in the chance of achieving clear or almost clear skin at week 16 a respondent was willing to accept for changes in other attributes. The 95% CIs for the MAD in achieving clear or almost clear skin at week 16 were obtained using the Delta method.[31]

Subgroup analyses were performed according to country (France, Spain, UK), age (<40, 40–50 and >50 years), gender (female, male), Patient Oriented Eczema Measure (POEM) overall score (0–7 (clear or almost clear/mild), 8–16 (moderate), 17-28 (severe/very severe))[32] and self-reported eczema severity (very mild/mild, moderate/severe/very severe).

Model selection

A number of different analyses were conducted as part of model selection. Given the DCE was conducted in different countries and the initial version of the survey was developed in the English language, the first analysis was related to the possibility of combining choice data from the different countries. The translation of the survey into different languages might have induced a translation effect, which could have resulted in systematic differences in the quality of the choice data across the countries. The results of this analysis indicated that differences in observed choices across countries could not be fully explained by potential changes in the underling quality of the choice data (online supplemental methods and table 2); as such, it was decided to pool country data and treat country of residence as a potential driver of heterogeneity in preferences alongside other personal characteristics.

The second analysis aimed to determine whether the standard MNL model would be appropriate to quantify average sample preferences. The MNL model was first compared with a mixed logit (MXL) model allowing for unobserved heterogeneity in preferences. Being the most flexible choice model, the MXL model was expected to statistically outperform the MNL model, but the objective of this analysis was to determine whether using a simpler model would lead to a biased measurement of sample preferences. The comparison of preference estimates between the two models showed a very high level of agreement (ie, very similar preferences identified with both models) (online supplemental methods and figure 1).

The MNL model was also compared with a nested logit (NL) model to determine whether the opt-out option 'old treatment' required different treatment to the other treatment alternatives. The NL model relaxed the hypothesis of independence of irrelevant alternatives, which is a core assumption of the MNL model and implies that all three treatment options were equally substitutable. Again, the comparison of preference estimates showed a high level of agreement between the MNL and NL models (online supplemental methods and figure 2). These results indicated that the MNL model provided an acceptable approximation of sample preferences.

Patient and public involvement

Cognitive pilot interviews were held with 15 patients to test understandability of the DCE survey. Other than participating in the DCE survey as respondents, patients were not involved in recruitment or study conduct. Investigators were blinded to the identities of the study participants, so the results of the study were not directly disseminated to them.

RESULTS

Participants

The DCE survey included 404 participants (114 in France, 145 in Spain and 145 in the UK) who were recruited between October and December 2019. Given recruitment for the quantitative online survey used patient panels and databases, 157 553 initial invites were sent, with a 4% (n=6287) response rate. The majority of the interested potential participants completed the screening questionnaire but were not eligible to participate, largely due to not having AD; 541 patients were eligible to participate, with 75% of those eligible completing the survey. Most participants were women (65%) with an average age of 44.1 years (table 2). Most participants were employed full time (56%) and had completed university education or higher (58%). The majority of participants had moderate-to-very severe AD according to POEM scores (62%) and self-reported eczema severity (67%) but good-to-excellent self-reported overall health (69%). Topical corticosteroids (66%) were the most frequently used class of medications at the time of the survey, followed by systemic immunosuppressant therapies (27%) and biologics (18%). Topical betamethasone (29%) and hydrocortisone (24%) were the most frequent currently used individual medications. Most patients (68%) had no prior experience of using self-injectable treatments for AD or any other illness.

Validity assessments

Overall, the survey sufficiently engaged participants: 89% selected the superior treatment option in the dominance test, 64% chose the same answers in the repeated choice task and 97% spent an adequate amount of time on the choice tasks (online

Table 2 Participant characteristics

Characteristic	N=404
Sex, n (%)	
Male	142 (35)
Female	262 (65)
Age, mean (SD)	44.1 (12.0)
Employment status	
Full time	227 (56)
Part time	75 (19)
Homemaker/housewife	21 (5)
Student	10 (2)
Unemployed	30 (7)
Retired	35 (9)
Disabled	12 (3)
Other	2 (0)
Education, n (%)	
No formal qualifications	1 (0)
Primary school or secondary education	38 (9)
College or some university	43 (11)
Completed vocational or professional certification	83 (21)
Completed university degree	148 (37)
Completed doctorate, post-doctorate, or equivalent	88 (22)
Other	3 (1)
Overall health, n (%)	
Excellent	20 (5)
Very good	96 (24)
Good	161 (40)
Fair	98 (24)
Poor	29 (7)
Prior experience with self-injectables (any)*	
Yes	129 (32)
No	275 (68)
Self-rated eczema severity, n (%)	
Very mild	19 (5)
Mild	116 (29)
Moderate	212 (52)
Severe	45 (11)
Very severe	12 (3)
POEM overall score, n (%)	
Clear or almost clear (0–2)	32 (8)
Mild eczema (3–7)	121 (30)
Moderate eczema (8–16)	192 (48)
Severe eczema (17–24)	47 (12)
Very severe eczema (25–28)	12 (3)
Class of AD medication currently used, n (%)†	
Topical corticosteroids	265 (66)
Topical calcineurin inhibitors	32 (8)
Phototherapy/UV treatment	20 (5)
Systemic immunosuppressant therapies	109 (27)
Biologics	72 (18)
Most frequently used current AD medications, n (%)†	
Betamethasone	119 (29)
Hydrocortisone	97 (24)
Prednisone	61 (15)
Clobetasol propionate	46 (11)

*Participants were not asked whether their prior use of self-injectables was for AD.
†Not mutually exclusive.
AD, atopic dermatitis; POEM, Patient Oriented Eczema Measure; UV, ultraviolet.

supplemental table 3). Also, for 90% of participants, decisions were not dominated by a single attribute and only 5% always chose the opt-out old treatment option. Participants were not excluded based on responses to the validity tests, following best practice recommendations,[33] as the preferences of patients may be valid and removal may induce selection bias.

Overall preferences for treatment attributes

The DCE data set had no missing values, as patients could not proceed in the survey without answering each question or item. If participants did not complete the survey they were not remunerated or included in the data set. Of the treatment attributes included in the DCE survey, participants most valued improving symptoms and reducing the risk of side effects (figure 2 and online supplemental table 4). The most valued change was an improvement from 20% to 50% in the chance of achieving a meaningful reduction in itch at week 16, although preferences did not significantly differ between an improvement to a 40% or 50% chance of achieving a meaningful reduction in itch. The next-most valued changes, in descending order, were a decrease in the risk of serious infections from 6% to 0%, a decrease in the risk of eye inflammation from 20% to 0% and an improvement in the chance of achieving clear or almost clear skin from 10% to 40%.

Participants also valued changes in the non-clinical attributes. The most valued change was switching from a treatment that can be used long-term but cannot be paused without affecting efficacy to one that can be used long-term with the possibility for pauses, without affecting efficacy.

An oral pill one time per day or two times per day was preferred over a subcutaneous treatment every 2 weeks, and a 2-day onset of action was preferred over a 2-week onset of action, although participants did not have a significant preference for a 1-week over a 2-week onset of action. Participants also preferred

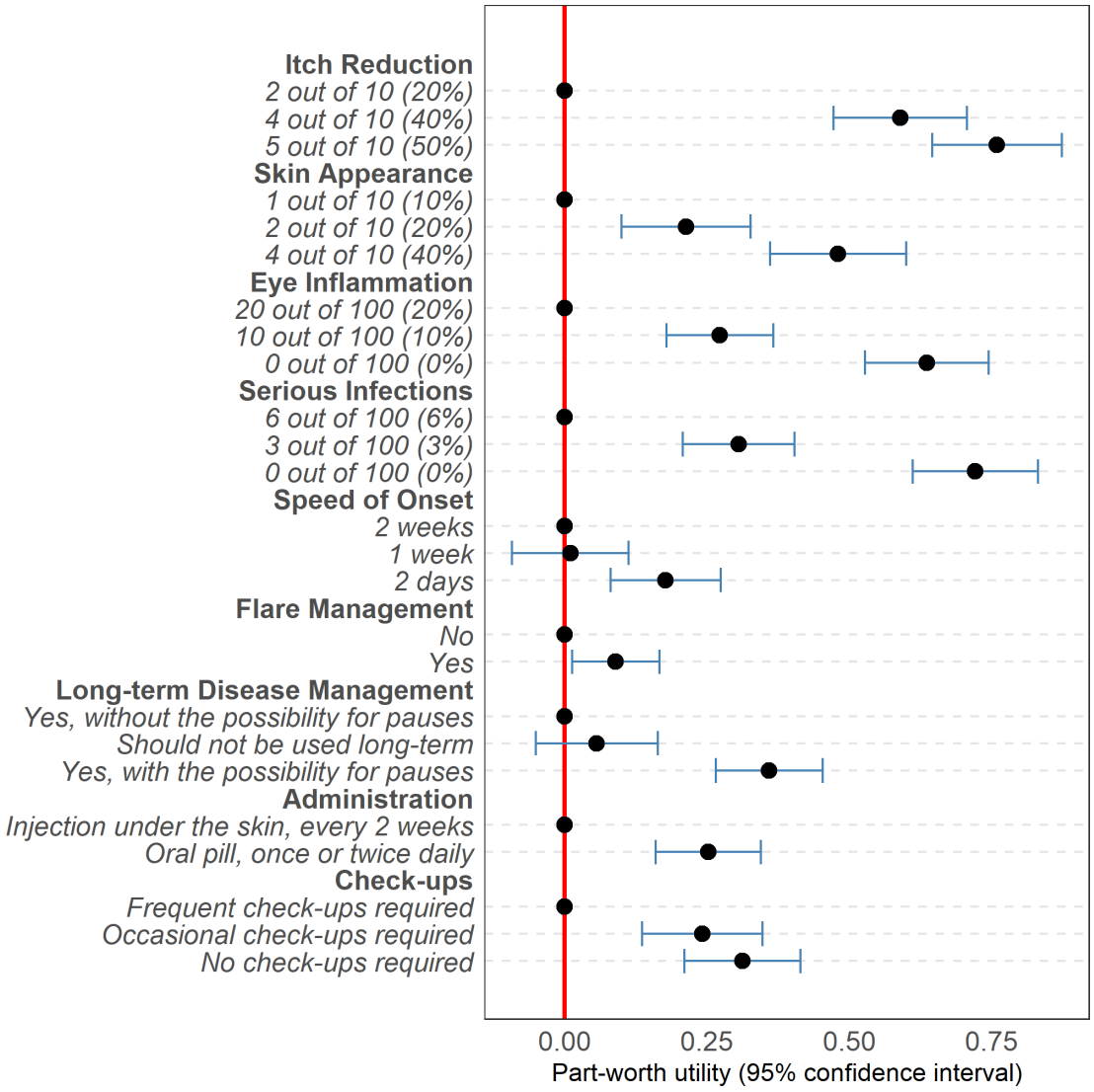


Figure 2 Multinomial logit results: part-worth utilities.

a treatment that can manage flares by modifying the dose according to symptoms over one that cannot be used to manage flares, although this was less important than changes in other non-clinical attributes.

Subgroup analyses

Results were similar for the three included countries (UK, Spain and France) (online supplemental figure 3), by age (online supplemental figure 4), by gender (online supplemental figure 5), by POEM overall score (online supplemental figure 6) and by self-reported eczema severity (online supplemental figure 7). However, those aged over 50 cared more about receiving an oral pill relative to those aged 40–50 years, for whom we did not detect a significant preference for administration.

Participants who had experience of self-injecting a treatment for any illness (32%) were more willing to accept a treatment that required a subcutaneous injection and placed less importance on reducing the risk of serious infections than those who did not have experience self-injecting a treatment for any illness (online supplemental figure 8).

Willingness to make trade-offs between treatment attributes

Participants would be willing to tolerate reduced efficacy to obtain changes in other treatment attributes. Specifically, they would be willing to tolerate a decrease in the probability of achieving clear or almost clear skin of 50.1% (95% CI, 38.5% to 61.8%) to increase the chance of achieving a meaningful reduction in itch at week 16 from 20% to 50%; 48.6% (95% CI, 35.2% to 62.0%) to reduce the risk of serious infections from 6% to 0%; and 42.3% (95% CI, 30.0% to 54.5%) to reduce the risk of eye inflammation from 20% to 0% (table 3). They would also be willing to tolerate a decrease in the probability of achieving clear or almost clear skin of 24.1% (95% CI, 16.5% to 31.6%) to switch from a treatment that can be used long-term but cannot be paused without losing efficacy to one that can be paused without losing efficacy; 16.6% (95% CI, 9.2% to 24.0%) to switch from

Table 3 Maximum acceptable decrease in the probability of achieving clear or almost clear skin at week 16

Attribute/level	Maximum acceptable decrease in the probability of achieving clear or almost clear skin (95% CI)
Itch reduction	
2 out of 10 (20%)	Reference
4 out of 10 (40%)	38.7 (28.8 to 48.6)
5 out of 10 (50%)	50.1 (38.5 to 61.8)
Eye inflammation	
20 out of 100 (20%)	Reference
10 out of 100 (10%)	17.9 (10.5 to 25.4)
0 out of 100 (0%)	42.3 (30.0 to 54.5)
Serious infections	
6 out of 100 (6%)	Reference
3 out of 100 (3%)	20.6 (12.7 to 28.6)
0 out of 100 (0%)	48.6 (35.2 to 62.0)
Speed of onset	
2 weeks	Reference
1 week	0.2 (–6.5 to 6.9)
2 days	11.3 (4.4 to 18.2)
Flare management	
No	Reference
Yes	5.8 (0.5 to 11.1)
Long-term disease management	
Yes, without the possibility for pauses	Reference
Should not be used long-term	4.3 (–2.7 to 11.3)
Yes, with the possibility for pauses	24.1 (16.5 to 31.6)
Administration	
Injection under the skin every 2 weeks	Reference
Oral pill one time or two times per day	16.6 (9.2 to 24.0)
Check-ups	
Frequent check-ups required	Reference
Occasional check-ups required	16.1 (8.7 to 23.5)
No check-ups required	20.9 (12.3 to 29.5)

a subcutaneous treatment every 2 weeks to an oral pill one time or two times per day; and 5.8% (95% CI, 0.5% to 11.1%) to obtain a treatment whose dosage can be modified to manage flares over one that cannot. Further, participants would be willing to tolerate a decrease in the probability of achieving clear or almost clear skin of 20.9% (95% CI, 12.3% to 29.5%) to switch from a treatment that requires frequent check-ups to one that does not require check-ups; and 16.1% (95% CI, 8.7% to 23.5%) to switch from a treatment that requires frequent check-ups to one that requires occasional check-ups.

DISCUSSION

The current study, which included 404 participants across the UK, France and Spain, found that adults with AD who had recently been treated with topical and/or systemic therapy most valued increasing the benefits and reducing the risks of their treatments, although attributes specific to new targeted therapies, such as mode of administration and long-term disease management, also had a significant effect on choices. Participants were willing to tolerate a significant decrease in the possibility of achieving clear or almost clear skin to obtain a treatment that is more convenient, including an oral pill one time or two times per day in place of a subcutaneous injection every 2 weeks, the ability to pause the treatment without losing efficacy, the ability to modify the dosage to manage flares and the possibility of requiring only occasional or no check-ups instead of frequent check-ups. Further, participants with self-injectable experience for any illness were more willing to accept self-injection than participants without self-injectable experience. However, 28% of participants were 'not willing' or 'somewhat not willing' to have a medication that required an injection for each dose. Preferences were similar between the three countries included (UK, France and Spain) and were largely unaffected by age or sex. In addition, preferences did not significantly differ based on disease severity, as measured using the POEM score, which is in line with prior research.[34]

Two other recent DCEs have examined the treatment preferences of patients with AD. Similar to our study, a DCE in the USA including 320 adults with moderate-to-severe AD[34] found that patients preferred an oral pill over subcutaneous injection and valued a rapid onset of action and increasing the chance of achieving clear or almost clear skin at week 16. A DCE including 323 patients in Japan ≥15 years of age with moderate-to-very severe AD and 121 dermatologists treating patients with AD[35] found that, as in the current study, both groups considered benefits and adverse effects the most important attributes of injectable treatments, although preferences for some treatment attributes differed between the groups. For example, patients placed more value on efficacy of improving rashes and treatment costs than dermatologists, while dermatologists valued time until response more than patients. Patients also preferred adding new treatments to current treatments as add-ons and receiving treatments at clinics, while physicians preferred reducing the number of current treatments and having patients self-administer at home. These differences in the preferences of patients and physicians emphasise the need for studies like the current one that are specifically designed to provide insight into patients' preferences.

Internal validity of the current DCE was examined using tests of choice stability and dominance, as well as by considering response times, health literacy and numeracy. The results were in line with existing research, including for choice stability[26] and suggested the survey sufficiently engaged participants. A potential limitation of this study is that the attributes and levels were not identified through

a separate qualitative research phase but rather through a targeted review of previous quantitative and qualitative studies of patients with AD and product labels for AD treatments. We do not expect that this influenced the results because the same attributes (onset of itch relief, probability of skin clearance, frequency or ease of administration/convenience and safety) were also identified through the qualitative phase of the US study.[34]

A potential limitation of this study is the inclusion of four probabilistic attributes, which increased the complexity of the study for participants. These were included to align with clinical data. To mitigate this, we included a thorough warm-up to the DCE with practice questions relating to the probabilistic attributes. In addition, a prior AD study included four probabilistic attributes (two probabilistic benefits and two probabilistic adverse events).[34] Another limitation of this study is that we used different denominators for probabilistic benefit and risk attributes. Different denominators were used to ensure participants could review all attribute information simultaneously while making their choices. However, using different denominators may have increased the study complexity and introduced a potential bias. Another potential limitation of this study is reference to the opt-out as 'old', which may have been perceived negatively. We used the terminology 'old' instead of current since we were aware that we were not presenting patients with their actual current treatments, which may have caused confusion. Due to the need to limit the participants' cognitive burden, not all potentially relevant attributes could be included in the DCE survey. However, cognitive pilot interviews of 15 patients with AD indicated that the attributes and levels were relevant and that no attributes were missing. Overall, participants also found the length and complexity of the survey acceptable. A further limitation is the inclusion of patients with non-severe AD, who would possibly not receive systemic therapies.[2] However, there is value in including these patients, because patients' disease severity may vary over time and treatment recommendations may change. Also, although few differences were found in preferences by age, sex or country, care should be taken when generalising to under-represented AD populations, such as patients with very severe AD, children or patients in lower-income countries. Additionally, since it is not culturally appropriate to ask about race in some European countries, data were not collected on this. We were therefore not able to determine whether this study represents the diverse ethnic groups in the study countries. Moreover, our sample included a high proportion of participants with university education and may therefore not be fully representative of the general AD population.

In conclusion, patients with AD most valued treatment benefits and reducing risks but were willing to accept a decrease in efficacy, as measured by the possibility of obtaining clear or almost clear skin at week 16, to obtain an oral treatment with a rapid onset of action. This information may help clinicians make shared decisions with patients about the most suitable treatment for AD. It can also support reimbursement applications, ensuring that health technology assessment decisions align with the preferences of individuals living with AD.

Acknowledgements Medical writing support was provided by Philip S Leventhal, PhD; Holly Richendrfer, PhD; and Stephen Gilliver, PhD of Evidera and was paid for by Eli Lilly & Co.

Contributors CT contributed to conception and planning of the study, acquisition and interpretation of the data and drafting and critical revision of the manuscript. AR contributed to conception and design of the study, interpretation of the data and critical revision of the manuscript. AW and J-PC contributed to design of the study, interpretation of the data and critical revision of the manuscript. NK contributed to analysis and interpretation of the data and critical revision of the manuscript. HK contributed to conception and design of the study and critical revision of the manuscript. TT contributed to conception and planning of the study, interpretation of the data and critical revision of the manuscript. TT is overall guarantor of the study. All authors approved the final version of the manuscript.

Funding This work was supported by Eli Lilly & Company. Grant/award number is not applicable.

Competing interests CT, NK, HK and TT are employees of Evidera, which was paid by Eli Lilly & Co for work related to this study. AR and J-PC are employees of Eli Lilly & Co. AW received personal fees from Eli Lilly & Co for work related to this study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The study was conducted according to good practice for stated preference research and was approved by Ethical & Independent Review Services (Independence, Missouri, USA; study number 19100-01). In addition, the study was conducted in accordance with International Council on Harmonisation Guidelines for Good Clinical Practice, the ethical principles of the Declaration of Helsinki, the European Union General Data Protection Regulation and all local laws and regulations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data sets generated and/or analysed during the study are not publicly available, because consent was not sought from participants to allow sharing of data with third parties.

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