Author’s response to reviews

Title: Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis

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Author’s response to reviews:

September 9, 2019

Nooshin Bagherani, Tehran University of Medical Sciences, Tehran, Iran
Associate Editor, BMC Dermatology
Dear Dr. Bagherani,

On behalf of my coauthors, I would like to thank you and the reviewers for their thoughtful comments on our manuscript titled “Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis” (BDER-D-19-00040R1).

Below are point-by-point responses addressing each comment. The manuscript has been revised with tracked changes and has been submitted, along with a clean version, for your consideration.

We hope that the revised manuscript is now acceptable for consideration of review and publication in BMC Dermatology.

Sincerely,

Laurent Eckert

Number) Reviewer comment

**Response/Location in manuscript:

1) Please add inclusion and exclusion criteria for selecting patients for your study from the RELIEVE-AD study

** The present study included patients on the RELIEVE-AD study who, on December 6, 2018, had completed the baseline (n=809) and Month 1 (n=391), 2 (n=343), 3 (n=289) and 6 (n=99) surveys.

Other criteria were the following:

• Age 18 years or older

• Can speak and read English

• Be willing to participate in the study and provide informed consent

• Have not previously participated in a dupilumab clinical trial
• Have not initiated treatment with dupilumab

/ (Page 6, Methods section, Data Source sub-section, paragraph 2, lines 2-5.)

2) Did you get consent from your subjects separate from the consent gotten in the RELIEVE-AD study? It is one of the most important issue you should consider.

** The patients consenting to the RELIEVE AD study did consent to fill the ADCT and that their data in aggregate form will be used for research purposes (see extract). As such we believe the current study is in the scope of the RELIEVE AD inform consent:

“Data from this survey will be used to better understand the treatment experiences of patients like you. Your participation in this study is completely voluntary and will not affect the care you receive from your physician or the support services from the DUPIXENT MyWay™ Patient Support Program. Any information collected will be treated as confidential and all results from this survey study will be reported in aggregate and for research purposes only.”

3) In the section “Data source”; please define the following terms with focusing on their scaling system: disease characteristics, symptoms and flares, AD control and AD-related overall health status, treatment satisfaction, and work productivity. I couldn’t find any precise definition and applicable system for scaling of these terms in your study.

** The surveys collected data on patient characteristics, including socio-demographics (age, sex, race/ethnicity, marital status, level of education, insurance, employment status, level of income, geographic region), medical history (self-reported age at AD diagnosis, comorbidities), and AD treatment and experience (treatment history prior to dupilumab initiation, concomitant therapy post dupilumab initiation, self-reported adherence to treatment and reasons for discontinuation), and treatment satisfaction. In addition, PROM data were collected using the Patient Global Assessment of Disease (PGAD), Numerical Rating Scale (NRS; patient self-reported symptoms [skin pain, burning, and sensitivity]; scores: 0–10; higher scores indicate worse symptom severity), disease control with ADCT (eczema-related symptoms, days with intense itching, overall bothersomeness, sleep problems, daily activities, mood/emotion; total score 0–24; higher scores indicate worse disease control), the Dermatology Life Quality Index (DLQI; health-related quality of life [HRQoL]; scores: 0–30; higher scores indicate worse HRQoL), and the Work Productivity and Activity Impairment-Atopic Dermatitis questionnaire (WPAI-AD; percentages 0–100; higher percentages indicate greater impairment) for patients in employment.

/ (Page 6, Methods section, Data Source sub-section, last paragraph and page 7 paragraphs 1, 2.)
4) In the “patient population”; again, because I don’t know what you meant by disease characteristic, I couldn’t understand “Overall, patient demographics and clinical characteristics were comparable between patients at baseline and those who had completed the follow-up surveys.”. In the statement ‘Overall, patient demographics and clinical characteristics were comparable between patients at baseline and those who had completed the follow-up surveys,’ ‘patient demographics and clinical characteristics’ has been replaced with ‘patient characteristics.’

** These characteristics (socio-demographics, medical history, etc.) are now clearly defined in the Data Source sub-section (page 6), eliminating any ambiguity in the interpretation of the statement in question. / (Page 11, Results section, Patient Population sub-section, paragraph 1, last 3 lines.)

5) Another vague point in this [above] sentence is that if you had done follow-up surveys for the patients eligible at the baseline, then those completed their surveys were subjects from the group of cases at baseline. Then, their demographic and characteristics information of these two groups (patients at baseline and those completed the surveys) should have been the same. Please explain.

** This sentence reflects the fact that the study was still ongoing at the time of the analysis and not all patients did report the data for all survey timepoints. Hence in order to assess whether the follow-up surveys were skewing the results in some way we assessed how the demographics changed over time.

6) Please explain the cause(s) of the decreased number of subjects in the later follow-ups.

** Regarding the sample size, the RELIEVE-AD study is ongoing, and the full dataset is still maturing; therefore, the reduction in patient numbers across follow-up periods was mainly due to the number of patients who became eligible for survey completion at those timepoints, as baseline surveys was completed at different timepoints. Patients were not necessarily completing all surveys; Unfortunately the drop-out rate is a limitation as is the fact that the study is still ongoing which means that we do not necessarily have the full data set present at each timepoint (some patients recruited late did not complete all survey timepoints / (Page 16, last paragraph, last 2 lines and page 17 first 2 lines.)

7) Please add the limitations of your study and your suggestion(s) for planning more robust studies in this field in the section “Conclusion”.
** We have added the following text: In consideration of our positive findings on the validity and reliability of the ADCT, a few study limitations are to be noted. First, participant diagnosis of AD relied only on self-report (i.e., not confirmed by a clinician). However, all included patients were prescribed dupilumab, which was approved only for AD when patients were enrolled in the study which should decrease the risk of mis-diagnosis. Another limitation is that the full dataset is still maturing i.e. some patients at the time of analysis did not report their data at all timepoints. In addition there were patients lost to follow up. However our results seem to behave well at different timepoints which is reassuring. Other studies currently ongoing will also confirm further the findings and address some of these limitations. One study is currently ongoing including patients and physicians to determine how ADCT compares to physician scales (EASI, physician assessment of control etc.) This study will as well confirm our findings in a population whom have a clear and robust diagnosis of AD. Another study is about to begin, to validate the ADCT in the EU region with data collected at 2 timepoints. We will hence further describe the validity of the ADCT across countries and time. / (Page 16, last paragraph, and page 17 first 2 lines.)

8) For preventing any problem in the “conflict of interest” issue, it would be ideal if academic-based persons to be lead and corresponding author. Please consider it and re-arrange the order of authors.

** Please see the change to the author order, which now lists Dr. Eric Simpson, as the lead author.

9) In this study, efficacy of a novel tool for patients' reporting evaluation of atopic dermatitis control is analyzed compared with the other patient-reported outcome measures, such as NRS, POEM, and DLQI. While the questionnaire, ADCT, can be a candidate of useful tool, several issue should be clarified in the revised version. I agree that ADCT can be reproducible and consistent with the other PROM. I am also interested in the correlation of ADCT and the objective evaluation score of AD severity, such as the physician's global assessment score, EASI, and SCORAD. Do the authors have any data presenting a possible correlation of ADCT and these objective measures?

** The correlation of ADCT with physicians assessment such as EASI and SCORAD are included in another study which is currently finishing recruitment (150 patients and physicians were recruited across 5 centers in the US for that purpose). The results of this additional study will be published as soon as the data are available and analyzed.
10) Patients who had been suffered from severe skin condition tend to score the condition better. The inconsistency of ADCT score and PGAD at baseline and month 1 might reflect the phenomenon. This can be a problem for evaluation of improvement of these patient-reported evaluation tools especially in the early phase. Do you have any comment about this?

** We have compared the psychometric properties of the ADCT with other general PROMs such as PGAD and dermatology-specific PROMs such as DLQI, and found that the ADCT displayed good reliability, validity and was able to detect changes. When we limited the analyses to uncontrolled patients (i.e., ADCT total score ≥ 7), the results did not change significantly. It is possible that patients who had suffered from severe skin condition tend to score the condition better, but it did not seem to significantly affect the results.

11) I would suggest that in the manuscript a list of the all lead and sub-investigators be included in order to recognize the physicians involved in the collection of the data. I would also suggest a copy of the ADCT be included as part of the manuscript.

** Our study used survey-based, patient-reported data from RELIEVE-AD to evaluate the psychometric properties of ADCT.

Patients were identified through enrolment in the Dupixent MyWay™ Patient Support Program in the US, and were recruited by Analysis Group, Inc. No physician was involved in the collection of data. A link to the ADCT (ADCT v1; https://patient-questionnaires.sanofi.com/questionnaires/adct-atopic-dermatitis-control-communication-tool) has been included in the Background section of the manuscript / (paragraph 3)

12) It is worth noting that this will insure all translations are available and to make sure that the public always get access to the right version the ADCT. This is now a recommended practice for PRO dissemination

** n/a

13) Please check references 29 and 36, they do not fit into the journal's style.

** References 29 and 36 have been updated to conform to journal’s style. / (Pages 8, 9)