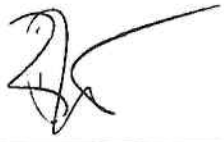
Study Report Template **Observational studies using pre-existing data without safety objectives** **(Cohort, Case-control or Cross-sectional studies using pre-existing data - chart reviews / claims or electronic healthcare databases / re-analyses of trial data / re-analyses of registry data)**	SANOFI **RDSD-002440**

Study Title: *A Retrospective study to analyse the treatment outcomes of patients with severe atopic dermatitis (AD) who were enrolled in the Early Access to Medicines Scheme (EAMS) for dupilumab.*		
Clubnet Reference Code: DUPILL09236		
Study Report Date / Status: 29/08/2018 / Complete		
Researcher: Rajesh Rout	**Therapeutic area:** Immunology	
Product Name / Compound #: Dupilumab	**Disease:** Atopic Dermatitis	

FINAL REPORT APPROVAL:

Study intended for submission to regulatory authorities (1) ☐ **Yes** ☒ **No**

If yes, the report must be approved by Pharmacovigilance and/or Regulatory Affairs representatives as appropriate

Name	**Signature**	**Date (dd/mm/yyyy)**
Study Manager Raj Rout, Medical Lead		**14/09/2018**
Evidence Leader (external to the study team) Richard Hudson, Principal Health Outcomes Manager		**17/09/2018**
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Other ad hoc members: Study Coordinator Lauren Davis, Scientific Advisor		**17/09/2018**

List of changes since previous version

Date (dd-mm-yyyy)	Change and rationale for change
n/a	N/a

Abbreviations

AD	Atopic Dermatitis
CRF	Case Report Form
EAMS	Early Access to Medicines Scheme
EASI	Eczema Area Severity Index
DLQI	Dermatology Quality of Life Index
HTA	Health Technology Assessment
IGA	Investigator Global Assessment
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NMA	Network Meta-Analysis
POEM	Patient Oriented Eczema Measure
PV	Pharmacovigilance
RGC	Research Governance Committee
SLR	Systematic Literature Review
TCS	Topical Corticosteroid
YHEC	York Health Economics Consortium

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1. SYNOPSIS	
Title of the study:	A Retrospective study to analyse the treatment outcomes of patients with severe atopic dermatitis (AD) who were enrolled in the Early Access to Medicines Scheme (EAMS) for dupilumab. (DUPILL09236)
Design:	Observational Studies based on secondary use of data Group E – Retrospective, multi-centre, descriptive observational study
Objectives:	Main Objectives: • To describe the change in EASI score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab • To describe the change in IGA score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab • To describe the change in DLQI & POEM score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab Other Objectives: • To qualitatively describe clinician opinion about patient response to dupilumab (from retrospective review of patient notes) • To report the proportion of patients who achieved a ≥4-point improvement in DLQI and EASI-50 scores (at 3 months and then at full available follow up-period). Safety follow-up was mandated by the MHRA for the duration of EAMS enrolment, data was collected by Pharmacovigilance (PV) proactively until Marketing Authorisation (MA). This retrospective study did not collect safety follow-up data, the raw data was provided to drug safety to review in the case of any adverse events reported inadvertently.
Population / Sample size:	The population included in this study was patients who were treated with dupilumab between 13th March 2017-18th April 2018. Sites were centres which had enrolled patients into the EAMS scheme, a total of 8/12 EAMS sites were included, based on results of a feasibility questionnaire and contractual agreement to participate at Trust level. Inclusion criteria: • Patient has received treatment with dupilumab for ≥3 months before the date of data collection as part of the Early Access to Medicines Scheme • Patient has consented to anonymised data being collected by Sanofi and selected third parties by signing the patient consent form at the start of EAMS • Patient has returned for at least one follow-up visit since initiation of treatment Exclusion criteria: • Patient has been on dupilumab <3 months before the date of data collection • Patient has not attended any follow-up visits • Patient has received treatment with dupilumab prior to EAMS e.g. previous enrolment in a dupilumab

	clinical trial EAMS inclusion criteria: For the purpose of EAMS, dupilumab was made available to adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies. Dupilumab could be used with or without topical corticosteroids.
Scientific committee and members:	**Medical Lead:** Raj Rout, Medical Lead Immunology **Study Coordinator:** Lauren Davis, Scientific Advisor, Immunology **RGC Committee members:** • Hubert Bland, Country Medical Chair/ DCV Head (Chair) • Gordon Boyd, SGZ Medical Head (RGC Voting Member) • Andy Hockey, GEM Medical Head (RGC Voting Member) • Mital Desai, CSU Head (RGC Voting Member) • John Solomon, PV Head (RGC Voting Member) • Claire Grant, HEOR Head (RGC Voting Member) • Graeme Esslemont, CSU Clinical Trial Regulatory Manager (RGC Voting Member) • Mital Desai, CSU Head (RGC Voting Member)
Introduction - **Background/rationale:**	• Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling and is indicated for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy. • The EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. • Dupilumab received EAMS designation on 13 March 2017. Dupilumab was made available to adult patients with severe AD who have failed to respond, or who are intolerant of, or ineligible for all approved therapies. Dupilumab can be used with or without topical corticosteroids. Enrolment ended at marketing authorisation on 27th September 2017. • Under the EAMS program, treatment was prescribed by physicians experienced in the treatment of dermatological conditions. • The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection. During EAMS dupilumab dosing was as per clinical practice and was not controlled by Sanofi. • EAMS patients were enrolled into the scheme independently by their treating clinician (no randomisation or intervention) • As part of entry into EAMS, three scores (Eczema Area and Severity Index (EASI)), DLQI, and IGA (Investigator Global Assessment) were collected on patient severity, to ensure that they were severe (as mandated by the EAMS “label”) before starting

	dupilumab. • Sanofi did not proactively initiate a study to collect outcome data for patients treated with dupilumab during EAMS, however, following a study feasibility analysis, it is evident that that clinicians collect severity scores for patients treated, as part of routine clinical practice (see feasibility below). Patient consent to collect baseline and outcome data for the purpose described was obtained at the start of EAMS. Only patients who signed the consent form will be included in the analysis. • Safety follow-up was mandated by the MHRA for the duration of EAMS enrolment, data was collected by Pharmacovigilance (PV) proactively until Marketing Authorisation (MA). This retrospective study did not collect safety follow-up data, the raw data was provided to drug safety to review in the case of any adverse events reported inadvertently. [MHRA website: Early access to medicines scheme (EAMS) scientific opinion: Dupilumab for treatment of dermatitis]. Accessed 13 February 2018. Available at https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-dupilumab-for-treatment-of-dermatitis [Dupilumab SPC] Accessed 13 February 2018. Available at: https://www.medicines.org.uk/emc/product/8553/smpc
Methodology:	This study was a retrospective review of the hospital medical notes, databases and electronic systems of eligible patients with AD who have received treatment with dupilumab through the EAMS for more than 3 months. Baseline patient data was available from EAMS entry forms held by Sanofi: • Patients were independently selected by the consultant in line with the EAMS indication, and applications were then reviewed and accepted by Raj Rout, Medical Lead. • Applications were received electronically from sites in a pseudo-anonymised format (initials and date of birth collected), once accepted, patients were assigned an EAMS reference number and applications were held by the medical team. • The baseline data will be used as a comparison with the follow-up data collected as part of this study. Follow-up data collection and analysis was conducted on behalf of Sanofi by the York Health Economics Consortium (YHEC), an independent healthcare research consultancy. YHEC contacted sites directly and providing a paper/electronic CRF. Data were collected in an anonymised format by members of the direct care team. Data were only collected for patients who consented at the start of EAMS. Data were limited to the dataset outlined in the protocol. Once data was collected, it was sent in an anonoymised format (EAMS reference number), to YHEC, an independent healthcare research consultancy for data management, analysis and report generation. This analysis comprises mainly descriptive statistics. Continuous variables were summarized in the main text using mean and standard deviation, with minimum and maximum values reported to provide the range. Appendix A

	provides a table including means, medians, modes, minimums, maximums, standard errors of the means, standard deviations, and interquartile ranges for all continuous variables. Categorical variables were summarized in the main text as frequency and proportion. Unplanned inferential statistics have been provided on request, primarily to assess the statistical significance of observed differences for the 16 $^{+/-4}$ weeks timeframe, for which the sample size was $n > 30$. For continuous scale variables a paired samples *t*-test was performed. For ordinal variables a Wilcoxon Signed Ranks test was performed. Pearson's correlations were performed to assess the relationships between different measures of severity. Correlation strength was interpreted in line with Mukaka (2012[1]; $r < 0.3$ = negligible; $r = 0.3$ to 0.5 =small; $r = 0.5$ to 0.7 = moderate; $r = 0.7$ to 0.9 = strong; $r = 0.9$ to 1.0 = very strong). No imputation was performed for missing data. Missing values were excluded from relevant analyses. Precise sample sizes are reported for each analysis.
Study time horizon:	This study includes EAMS data covering the period from the initiation of the EAMS period (13th March 2017 to 18th April 2018)

[1] Mukaka MM. A guide to appropriate use of correlation coefficient in medical research. Malawi Medical Journal. 2012;24(3):69-71.

RESULTS	
Interim analysis	The results of the interim analysis conducted in April 2018 are presented in Appendix B. The interim analysis reported only on objectives which were required for the response to the NICE appraisal consultation document in April 2018. Following the interim analysis, a further case report was received and results were re-analysed to include the full data set, and to fulfil all objectives of the retrospective study.
Number of Participants:	CRFs were returned for a total of 65 patients. Four were excluded because no date of first injection was provided, preventing analysis of time since injection. A further three were excluded because no follow-up data was recorded, and one was excluded because no baseline data was available, preventing comparison between baseline and follow-up. The total analysis dataset comprised 57 patients.
Participant characteristics and primary analyses:	**Participant characteristics** The analysis dataset included a total of 57 patients, comprising 20 (35.1%) females, 36 males (63.2 %) with a mean age of 41.2 years (SD: 14.21 years; range: 20 to 76 years); there was one patient for whom gender was not reported and two for whom age was not reported. Past immunosuppressant use was reported for 91.2% (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different types of immunosuppressant. The most common immunosuppressants prescribed were azathioprine (81.0%; 47 patients) and ciclosporin (86.2%; 50 patients). Immunosuppressant use at the time of enrolment was reported for 54.4% (31 patients) of the follow-up sample, of which 1.8% (1 patient) was reported to be on two immunosuppressants, and 52.6% (30 patients) were reported to be on one immunosuppressant medication. In these patients, ciclosporin was most common (19.0%; 11 patients), followed by methotrexate (15.5%; 9 patients). EASI, IGA and DLQI scores indicated that, on average, patients were rated as having severe AD that had a large impact on their quality of life at baseline. **Primary analyses** In line with the objectives stated, the key results were as follows. On average, AD severity, as measured by both EASI and IGA scales, decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. EASI scores improved by a mean of 14.13 points, or 56%, with two thirds of patients (66.7%) demonstrating a reduction of 50% or more (meeting the EASI-50 criteria), and 73% demonstrating a minimally clinically important difference of 6.6 points or more. IGA scores improved by at least two categories for 75% patients, and by one category for 17.9%, with no change for one patient and an increase in severity for one patient. On average, the impact of AD on patients' lives, as measured by the DLQI, also decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. DLQI scores improved by a mean of 8.98 points, or 59%, with 80% patients demonstrating a minimally

	clinically important improvement of at least 4 points. 53% patients reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores. For 85% patients, clinicians rated the treatment response as being either ‘better’ (19%) or ‘much better’ (65%). Analysis of changes in AD severity, quality of life and response to treatment other timeframes demonstrated similar results but interpretation is limited due to small sample sizes.

Other analyses:	Due to timelines required for reporting, an interim analysis was conducted in April 2018 (results presented in Appendix B). The interim analysis reported only on objectives which were required for the response to the NICE appraisal consultation document. Following the interim analysis, a further case report was received and results were re-analysed to include the full data set, and to fulfil all objectives of this retrospective study. It was anticipated that data collected would be consistent across sites, with a follow-up date for all patients at 3 months from baseline from which key analyses could conducted. However, due to inconsistencies and overlap between follow-up time periods across and within sites, follow-ups were recategorised as described in Section 4.5. The main analyses were conducted for the 16 $^{+/-4}$ week timeframe. Analyses at other timeframes were reported for completeness. On request, inferential statistics were included where sample sizes were sufficient (*n*= approximately 30) to assess the statistical significance of change from baseline.
Discussions:	(a) Key results In line with the objectives stated, the key results were as follows. On average, AD severity, as measured by both EASI and IGA scales, decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. EASI scores improved by a mean of 14.13 points, or 56%, with two thirds of patients (66.7%) demonstrating a reduction of 50% or more (meeting the EASI-50 criteria), and 73% demonstrating a minimally clinically important difference of 6.6 points or more. IGA scores improved by at least two categories for 75% patients, and by one category for 17.9%, with no change for one patient and an increase in severity for one patient. On average, the impact of AD on patients' lives, as measured by the DLQI, also decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. DLQI scores improved by a mean of 8.98 points, or 59%, with 80% patients demonstrating a minimally clinically important improvement of at least 4 points. 53% patients reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores. For 85% patients, clinicians rated the treatment response as being either 'better' (19%) or 'much better' (65%). Analysis of other timeframes demonstrated similar results but interpretation is limited due to small sample sizes. (b) Interpretation This is the first UK real world analysis of treatment outcomes for patients treated with dupilumab in clinical practice. We observed a statistically significant improvement in AD disease severity as measured by EASI and IGA between baseline and a 16 $^{+/-4}$ week follow-up period, with two thirds

of patients (66.7%) demonstrating a reduction of 50% or more (meeting the EASI-50 criteria).

On average, the impact of AD on patients' lives, as measured by the DLQI, also decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up.

53% patients reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores. Our economic model used 16 weeks as the timepoint for assessment of response; these data suggest that responses are seen earlier.

Most clinicians rated the treatment response as being either 'better' or 'much better' after treatment with dupilumab.

This data supports the use of dupilumab in a clinical practice setting.

Table 5. Patients meeting EASI-50 response criteria in RCTS compared to real-world EAMS study Clinical setting

Clinical Setting	Q2W dosing (n)	EASI-50
CHRONOS trial (at 16 weeks)	106	80%
CAFÉ trial (at 16 weeks)	107	85%
EAMS (at 16 weeks +/- 4 weeks)	35	66.7%

Note that this data was collected retrospectively outside of a controlled setting, and there were differences in patient baseline characteristics, therefore data must not be directly compared with results from other studies including the pivotal trials.

These emerging data from EAMS provide further support of dupilumab sustained benefit. Furthermore, past immunosuppressant use was reported for 91.2% of EAMS patients (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different types of immunosuppressant. The EAMS patients are real world patients who were more likely to have complicating issues and difficult-to-treat disease.

(c) Generalisability

This study included data from 57 patients from 8/12 UK EAMS centres.The entry criteria into the dupilumab EAMS was stricter than the licensed indication of dupilumab therefore results are not generalisable to the population of patients who may be prescribed dupilumab in the real world. Patients enrolled into EAMS were generally more severe, with the majority of patients having failed on more than one systemic immunosuppressant prior to commencing treatment with dupilumab. Regardless of this, the HRA re-

	classified the study as research on the basis that the findings would contribute to support dupilumab as part of the HTA. (d) Limitations This study is limited by the lack of control group, lack of randomization and the completeness of data available. Due to the volume of missing data, no imputations were performed. Due to small sample sizes the majority of analyses were descriptive only. It is possible that patients without follow-up data were more likely to be those who had not responded as well to treatment.
Conclusions:	The key conclusion of the study is that use of dupilumab improves signs and symptoms of atopic dermatitis, and the impact that AD has on quality of life in a real-world setting which is the first of its kind in the UK. This is of particular significance given that the EAMS patients had severe disease at baseline that was hard to treat.
Date of report:	29/08/2018

2. BACKGROUND

Background / Introduction

- Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling and is indicated for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.
- The efficacy and safety of Dupilumab as monotherapy and with concomitant topical corticosteroids were evaluated in three pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, and CHRONOS) in 2119 patients 18 years of age and older with moderate to severe atopic dermatitis (AD) defined by Investigator's Global Assessment (IGA) score ≥3, an Eczema Area and Severity Index (EASI) score ≥16, and a minimum body surface area (BSA) involvement of ≥10 %. Eligible patients enrolled into the three studies had previous inadequate response to topical medication.
- The CAFE study evaluated the efficacy of Dupilumab compared to placebo during a 16-week treatment period, administered with concomitant TCS, in adult patients with AD who are not adequately controlled with, or are intolerant to, oral ciclosporin, or when this treatment is currently contraindicated or not medically advisable. A total of 325 patients were enrolled, with 210 patients who were previously exposed to ciclosporin and 115 patients who have never been exposed to ciclosporin because ciclosporin treatment was medically inadvisable.
- The medical rationale for this study is to further the understanding about the efficacy of dupilumab in a real world clinical setting. This data can be used to support the HTA submission for dupilumab.
- The MHRAs Early Access to Medicines Scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.
- Dupilumab received EAMS designation on 13 March 2017. Dupilumab was made available to adult patients with severe AD who have failed to respond, or who are intolerant of or ineligible for all approved therapies. Dupilumab can be used with or without topical corticosteroids. Enrolment ended at marketing authorisation on 27th September 2017.
- EAMS patients were enrolled into the scheme independently by their treating clinician (no randomisation or intervention)
- As part of entry into EAMS, three scores (Eczema Area and Severity Index (EASI)), DLQI, and IGA (Investigator Global Assessment) were collected on patient severity, to ensure that they were severe (as mandated by the EAMS “label”) before starting dupilumab.
- Sanofi did not proactively initiate a study to collect outcome data for patients treated with dupilumab during EAMS, however, following a study feasibility analysis, it is evident that that clinicians collect severity scores for patients treated, as part of routine clinical practice (see feasibility below). Patient consent to collect baseline and outcome data for the purpose

described was obtained at the start of EAMS. Only patients who signed the consent form will be included in the analysis.

3. RESEARCH QUESTIONS AND STUDY OBJECTIVES

The purpose of this study was to assess the efficacy outcomes of treatment with dupilumab in a real-world clinical setting. The study included patients who had been deemed as 'severe' by their clinician, based on their treatment history and current symptoms.

Main Objectives:

- To describe the change in EASI score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab
- To describe the change in IGA score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab
- To describe the change in DLQI & POEM score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab

Other Objectives:

- To qualitatively describe clinician opinion about patient response to dupilumab (from retrospective review of patient notes)
- To report the proportion of patients who achieved a ≥4-point improvement in DLQI and EASI-50 scores (at 3 months and then at full available follow up-period).

3.1. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	February 2018	Ethical Considerations	Updated to include HRA approval (study reclassification to 'research')	The HRA re-classified this study to 'research' after commencement, due to potential generalisability of results. The study was subsequently reviewed and approved by the HRA.

4. RESEARCH METHODS

4.1. Study design

A 'Group E' observational, multi-centre, retrospective study conducted across 8/12 EAMS centres in the UK. The study analysed the treatment outcomes (as assessed by AD severity scores) of eligible patients with severe AD, compared to baseline.

Primary Objective:

- To describe the change in EASI score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab
-

Other Objectives:

- To describe the change in IGA score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab
- To describe the change in DLQI & POEM score compared to baseline (EAMS enrolment) in patients who have received ≥ 12 weeks of treatment with dupilumab
- To qualitatively describe clinician opinion about patient response to dupilumab (from retrospective review of patient notes)
- To report the proportion of patients who achieved a ≥4-point improvement in DLQI and EASI-50 scores (at 3 months and then at full available follow up-period).

4.2. Setting

This was a retrospective analysis of data; all 12 NHS sites that had enrolled patients into EAMS had the opportunity to participate. Sites were included depending on the following:

- Their ability to collect data within the stated timelines for collection
- The site having patients who have completed ≥3 months of treatment with dupilumab since the start of EAMS
- The site having collected follow-up data
- Patients having signed the consent form at the start of EAMS allowing data to be analysed by Sanofi and selected third parties
- Obtaining local hospital R&D approval

Follow-up data were collected from a total of 8 sites between 13th March 2018 and April 18th 2018.

4.3. Data sources and measurement

All data were entered onto data collection forms from electronic health records by study site contacts at each site. 'Back-to-back' data monitoring, whereby study site contacts with access to patient records verbally confirmed the accuracy of the data received at the analysis site, item by item, via the telephone, was completed for 10 of the 57 patients for whom baseline and follow-up data were available (18%). No errors were identified within this sample.

The following variables were captured at baseline:

- Patient demographics:
  - Age (years);
  - Sex;
- Past and current AD treatments by class and active ingredient:
  - Immunosuppressants (e.g. azathioprine, methotrexate);

The following data were captured at both baseline and follow-up:

- Atopic dermatitis (AD) scores (at intervals by patient follow-up date):
  - EASI score (eczema area and severity index; possible scores range from 0 to 72, where higher scores indicate greater severity AD);
  - IGA score (investigator's global assessment score; possible scores range from 0 to 4, where higher scores indicate greater severity AD);
  - DLQI score (dermatology life quality index; possible scores range from 0 to 30, where higher scores indicate greater impact of AD on quality of life);
  - POEM score (patient-oriented eczema measure; possible scores range from 0-28, where higher scores indicate greater symptom burden).

The following variable was captured at follow-up only:

- Response to treatment:
  - A narrative was provided on patient response to treatment as recorded in the patient notes. These notes were mapped to a 5 point Likert scale by the clinician.

4.4. Subjects

This was a retrospective analysis of data from patients already enrolled in EAMS who have received ≥3 months of treatment with dupilumab since baseline (treatment initiation). Patients were selected by the clinician.

Inclusion criteria:

- Patient has received treatment with dupilumab for ≥3 months before the date of data collection as part of the Early Access to Medicines Scheme
- Patient has consented to anonymised data being collected by Sanofi and selected third parties by signing the patient consent form at the start of EAMS
- Patient has returned for at least one follow-up visit since initiation of treatment

Exclusion criteria:

- Patient has been on dupilumab <3 months before the date of data collection
- Patient has not attended any follow-up visits
- Patient has received treatment with dupilumab prior to EAMS e.g. previous enrolment in a dupilumab clinical trial

All eligible patients for whom data were available to York Health Economics Consortium (YHEC) on 18th April 2018 were included in the dataset.

4.5. Variables

Medicinal product:

- Dupilumab 300 mg solution for injection in pre-filled syringe
- The recommended dose of Dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection.
- Dupilumab was overseen by a consultant dermatologist and wad administered according to clinical practice, with no control by Sanofi (retrospective analysis only)
-

Baseline characteristics for analysis and stratification:

- Age
- Gender
- Immunosuppressant use at enrolment

Outcome variables for analysis:

- EASI score
    - Raw score
    - Categorical score (see Section 4.5 for more details)
    - Achievement of MCID (see Section 4.5 for more details)
    - Achievement of EASI-50 (see Section 4.5 for more details)
- IGA score
    - Magnitude of change (see Section 4.5 for more details)
- DLQI score
    - Raw score
    - Categorical score (see Section 4.5 for more details)
    - Achievement of MCID (see Section 4.5 for more details)

4.6. Study size

Study size was determined by the number of eligible patients for whom data were available to YHEC on 18th April 2018. Data were available for a total of 65 patients. Of these, a recorded date of injection (necessary for calculating follow-up periods) was provided for 61 patients. Of these, no follow-up data were recorded for 3 patients, and no baseline data were recorded for 1 patient. As such, the analysis dataset included data from a total of 57 patients.

4.7. Data management and transformation

Data collection and analysis was conducted on behalf of Sanofi by the York Health Economics Consortium (YHEC), an independent healthcare research consultancy. YHEC contacted sites directly to provide a paper/electronic CRF. Data were collected in an anonymised format by members of the

direct care team. Data was only collected for patients who had consented at the start of EAMS. Data was limited to the dataset outlined in the protocol. Once data were collected, it was sent in an anonoymised format (EAMS reference number), to YHEC, an independent healthcare research consultancy, for data management, analysis and report generation.

All EAMS data available to YHEC on 18 April 2018 were entered by a single researcher into separate Excel templates for baseline and follow-up data. Where appropriate, for continuous variables, conditional formatting was used to highlight unexpected entries (i.e. entries outside the possible range of values), and for categorical inputs, drop-down boxes were used to ensure consistency of input.

Where required, IGA ratings were recoded. Ratings of '5' were assumed to be indicative of use of a different rating scale, where a score of 5 reflects most severe disease, and as such, these ratings were re-categorised as '4'. Ratings across categories (e.g. a rating of 3 to 4) were assumed to reflect a severity that the clinician did not persistently consider in the higher category, and thus re-categorised at the lower score. EASI and DLQI scores for one patient were rated as '>35' and '>25' respectively. Under the assumption that the clinician regarded AD severity as greater than these values, but not persistently at a specific higher score, these were conservatively recoded as 36 and 26.

Follow-up data were categorised by date since injection into the following timeframes;

- 2 to 4 weeks (14 to 27 days)
- 4 to 8 weeks (28 to 55 days)
- 8 to 12 weeks (56 to 83 days)
- 12 to 20 weeks (84 to 139 days; also referred to as 16 $^{+/-4}$ weeks)
- 20 weeks or more (140 days+)

Response-to-treatment data were not always collected at the same timepoints as severity scales and in some instances more than one score was provided within a single timeframe. In instances where the two ratings from the same period conflicted (*n*=6), the later dated measurement was used for the analysis dataset regardless of the magnitude of the value, to better reflect the long-term impact of the course of treatment. For the severity scales there were no instances where more than one of each measurement was recorded within any timeframe.

The main analysis was conducted on the 12 to 20 week timeframe, which corresponds to 16 $^{+/-4}$ weeks and is aligned with cut-offs in clinical trials. Analyses of data for other timeframes was conducted to provide a fuller indication of change. Table 1 shows that, on average, measurements in the first (2 to 4 week) timeframe were taken at around 2 and a half weeks from first injection; in the second (4 to 8 week) timeframe, just over four weeks from first injection; in the third (8 to 12 week) timeframe, around nine weeks from first injection; the fourth (16+/- 4 weeks) timeframe, at around 14 weeks from first injection; and measurements in the final (20 weeks or more) timeframe were taken at around 26 weeks from first injection.

Table 1 Average number of days between first injection and outcome measurement for each timeframe

Timeframe	**Days between first injection and outcome measurement**			
	Minimum	**Maximum**	**Mean (SD)**	**Median**
2 to 4 weeks (*n*=30)	14	27	17.9 (4.4)	16
4 to 8 weeks (*n*=19)	28	49	33.8 (7.6)	29
8 to 12 weeks (*n*=19)	56	83	64.5 (8.9)	63
12 to 20 weeks (*n*=39)	84	133	103.8 (14.8)	100
20 weeks or more (*n*=12)	140	294	184.3 (42.0)	181

Data were then exported into SPSS (V 24.0) for analysis.

Age was categorised into the following groups for result stratification:

- Young adults: 18 to 35 years;
- Middle-aged adults: 36 to 55 years;
- Older adults: 56 years and over.

Immunosuppressant use at the time of enrolment was categorized as a dichotomous yes/no variable for result stratification.

Dermatitis scores for each timeframe were categorised as follows:

- IGA scores:
  - 0 = Clear;
  - 1 = Almost clear;
  - 2 = Mild disease;
  - 3 = Moderate disease;
  - 4 = Severe disease.
- EASI scores (as per Lesham et al., 2015[2]):
  - 0 = Clear;
  - 0.1 to 1.0 = Almost clear;
  - 1.1 to 7.0 = Mild disease;
  - 7.1 to 21.0 = Moderate disease;
  - 21.1 to 50.0 = Severe disease;
  - 51.0 to 72.0 = Very severe disease.
- DLQI scores (as per Hongbo et al., 2005 [3]):
  - 0 to 1 = No effect on patient's life;
  - 2 to 5 = Small effect on patient's life;
  - 6 to 10 = Moderate effect on patient's life;
  - 11 to 20 = Very large effect on patient's life;
  - 21 to 30 = Extremely large effect on patient's life.

Variables reflecting changes in dermatitis scores from baseline were computed for each timeframe as follows:

- IGA scores
  - Worse (any move from a less severe category at baseline to a more severe category at follow-up)
  - No change (no change in severity of category between baseline and follow-up)
  - Improvement by one category (any move from a more severe category at baseline to a category one grade less severe at follow-up)
  - Improvement by two categories or more (any move from a more severe category at baseline, to a category at least two grades less severe at follow-up)
- EASI scores:
  - Absolute change (raw score at baseline minus raw score at follow-up; a positive value indicates a reduction in severity)
  - Percentage change (score at follow-up as a percentage of the score at baseline; a positive value indicates a reduction in severity)
  - EASI-50 (a dichotomous yes/no variable indicating whether the score at follow-up reflects at least a 50% reduction compared with the score at baseline)

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[2] Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. British Journal of Dermatology. 2015 May 1;172(5):1353-7.

[3] Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean?. Journal of Investigative Dermatology. 2005 Oct 31;125(4):659-64.

    - Minimally clinically important difference (MCID; a dichotomous yes/no variable indicating whether the score at follow up reflects at least a 6.6 point reduction (as established in Schram et al. 2012[4]) compared with the score at baseline)
- DLQI scores:
    - Absolute change (raw score at baseline minus raw score at follow-up; a positive value indicates a reduction in severity)
    - Percentage change (score at follow-up as a percentage of the score at baseline; a positive value indicates a reduction in severity)
    - MCID (a dichotomous yes/no variable indicating whether the score at follow up reflects at least a 4 point reduction (as established in Basra et al., 2015[5]) compared with the score at baseline)

The following variables collected at baseline from EAMS enrolment forms were not analysed in this study: weight, height, past AD treatments by class and active ingredient, AD treatments at the time of enrolment by class and active ingredient.

POEM scores were collected only from one site, therefore these data were not reported.

4.8. Statistical methods

4.8.1. *Main summary measures*

Continuous variables were summarized in the main text using mean and standard deviation, with minimum and maximum values reported to provide the range. Appendix A provides a table including means, medians, modes, minimums, maximums, standard errors of the means, standard deviations, and interquartile ranges for all continuous variables. Categorical variables were summarized in the main text as frequency and proportion.

4.8.2. *Main statistical methods*

This observational study reports mainly descriptive statistics. Unplanned inferential statistics have been provided on request, primarily to assess the statistical significance of observed differences for the 16 $^{+/-4}$ weeks timeframe, for which the sample size was $n > 30$. For continuous scale variables a paired samples *t*-test was performed. For ordinal variables a Wilcoxon Signed Ranks test was performed.

Pearson's correlations were performed to assess the relationships between different measures of severity. Correlation strength was interpreted in line with Mukaka (2012[6]; $r < 0.3$ = negligible; $r = 0.3$ to 0.5 =small; $r = 0.5$ to 0.7 = moderate; $r = 0.7$ to 0.9 = strong; $r = 0.9$ to 1.0 = very strong).

4.8.3. *Bias and confounding*

No methods were employed to reduce potential sources of bias. Main results were reported for the full sample, and also split by characteristics such as past medication use and sociodemographic characteristics that may confound the results.

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[4] Schram ME, Spuls PhI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minmal clinically important difference. European Journal of allergy and Clinical Immunology. 2012; 67: 99-106.

[5] Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. Dermatology. 2015; 230(1): 27-33

[6] Mukaka MM. A guide to appropriate use of correlation coefficient in medical research. Malawi Medical Journal. 2012;24(3):69-71.

4.8.4. *Missing values*

No imputation was performed for missing data. Missing values were excluded from relevant analyses. Precise sample sizes are reported for each analysis.

4.8.5. *Sensitivity analyses*

No sensitivity analyses were performed.

4.8.6. *Amendments to the statistical analysis plan*

It was anticipated that data collected would be consistent across sites, with a follow-up date for all patients at 3 months from baseline from which key analyses could conducted. However, due to inconsistencies and overlap between follow-up time periods across and within sites, follow-ups were recategorised as described in Section 4.5. The main analyses were conducted for the 16 $^{+/-4}$ week timeframe. Analyses at other timeframes were reported for completeness.

POEM scores were collected only from one site, therefore these data were not reported.

On request, inferential statistics were included where sample sizes were sufficient (*n*= approximately 30) to assess the statistical significance of change from baseline.

4.8.7. *Quality control*

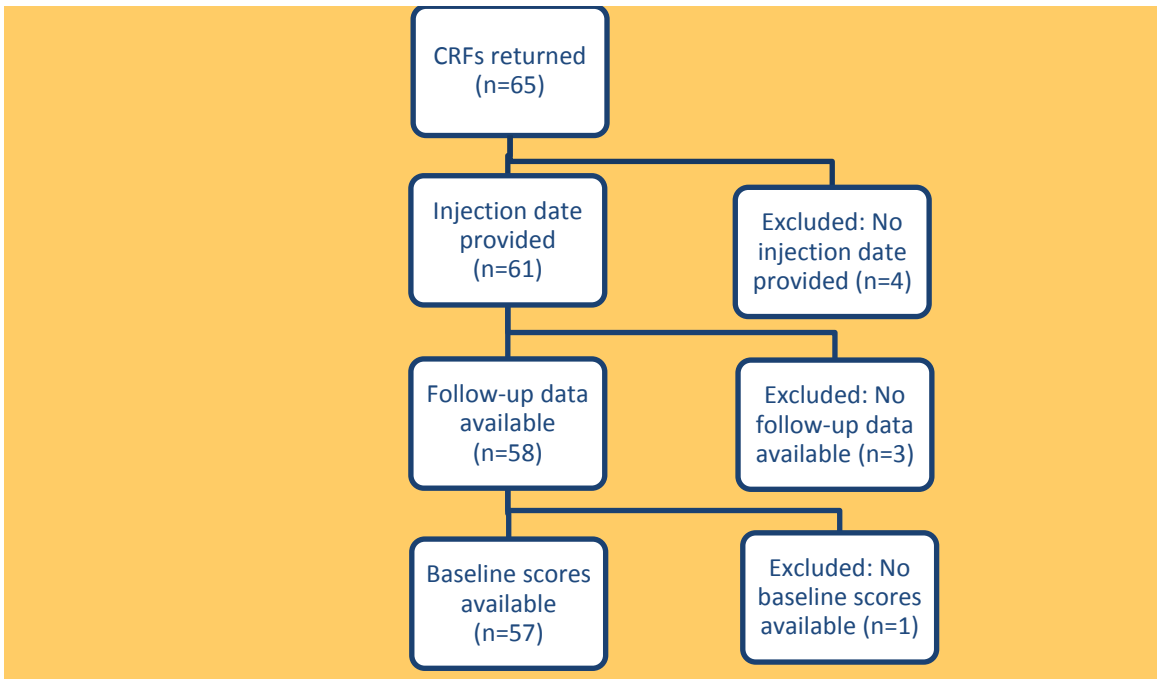
Analyses were sense-checked and transcription errors reviewed by a second researcher.

5. RESULTS

5.1. Participants

Figure 1 depicts the number of patients for whom data were available, exclusions and reasons for exclusions. The analysis dataset included a total of 57 patients. Due to inconsistency of measurement, data were missing for many analyses. All missing data was excluded from the relevant analysis and exact numbers of participants included within each analysis are reported throughout.

Figure 1 *Diagram demonstrating flow of excluded and included patient data*



5.2. Baseline characteristics

The analysis dataset included a total of 57 patients, comprising 20 (35.1%) females, 36 males (63.2 %) with a mean age of 41.2 years (SD: 14.21 years; range: 20 to 76 years), one patient for whom gender was not reported and two for whom age was not reported.

5.2.1. *Immunosuppressant use at baseline*

Past immunosuppressant use was reported for 91.2% (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different types of immunosuppressant. The most common immunosuppressants prescribed were azathioprine (81.0%; 47 patients) and ciclosporin (86.2%; 50 patients).

Immunosuppressant use at the time of enrolment was reported for 54.4% (31 patients) of the follow-up sample, of which 1.8% (1 patient) was reported to be on two immunosuppressants, and 52.6% (30 patients) were reported to be on one immunosuppressant medication. In these patients, ciclosporin was most common (19.0%; 11 patients), followed by methotrexate (15.5%; 9 patients).

Table 2 reports detailed immunosuppressant use statistics.

Table 2 Immunosuppressant use in the sample

	Frequency of patients with reported past use	**Frequency of patients with reported use at the time of enrolment**
Type of immunosuppressant		
Any	**52 (91.2%)**	**31 (54.4%)**
Azathioprine	47 (81.0%)	5 (8.6%)
Ciclosporin	50 (86.2%)	11 (19.0%)
Mycophenolate mofetil	28 (48.3%)	6 (10.3%)
Methotrexate	41 (70.7%)	9 (15.5%)
Leflunomide	1 (1.7%)	1 (1.7%)
Other (unspecified)	1 (1.7%)	0
Number of immunosuppressants		
None	5 (8.6%)	26 (45.6%)
One	2 (3.5%)	30 (52.6%)
Two	7 (12.3%)	1 (1.8%)
Three	21 (36.8%)	0
Four	21 (36.8%)	0
Five	1 (1.8%)	0

5.2.2. *EASI scores at baseline*

EASI baseline scores were not reported for 2 members of the follow-up sample. For the remaining sample (*n*=55), baseline EASI scores ranged from 4.3 (mild disease) to 72.0 (very severe disease), with both the most common category being severe disease, and the sample mean values for the full cohort (27.93, SD = 13.09) and all stratifications (see Table 3) corresponding to a rating of severe disease.

Table 3 EASI scores at baseline

	Stratification			
	All (*n*=55)	**Age group**	**Immunosuppressant use at enrolment**	**Gender**

Statistic	Measure		Younger Adults (*n*=14)	Middle-aged Adults (*n*=18)	Older Adults (*n*=22)	No (*n*=26)	Yes (*n*=29)	Female (*n*=19)	Male (*n*=36)
Mean (SD)	**EASI score at baseline**	27.93 (13.09)	26.00 (14.12)	24.48 (12.77)	31.43 (12.37)	29.99 (14.62)	26.09 (11.50)	24.41 (12.65)	29.79 (13.11)
Frequency (n, % within stratification group)	**EASI scores 'clear' at baseline**	0	0	0	0	0	0	0	0
	EASI scores 'almost clear' at baseline	0	0	0	0	0	0	0	0
	EASI scores 'mild' at baseline	2 (3.7%)	1 (7.1%)	1 (5.6%)	0	0	2 (6.9%)	0	2 (5.6%)
	EASI scores 'moderate' at baseline	13 (24.1%)	4 (28.6%)	6 (33.3%)	3 (13.6%)	7 (26.9%)	6 (20.7%)	7 (36.8%)	6 (16.7%)
	EASI scores 'severe' at baseline	38 (69.1%)	8 (57.1%)	11 (81.8%)	18 (81.8%)	17 (65.4%)	21 (72.4%)	11 (57.9%)	27 (75.0%)
	EASI scores 'very severe' at baseline	2 (3.7%)	1 (7.1%)	0	1 (4.5%)	2 (7.7%)	0	1 (5.3%)	1 (2.8%)

Note: Age was not reported for one patient.

5.2.3. *IGA scores at baseline*

IGA baseline scores were not reported for 6 members of the follow-up sample. For the remaining sample (*n*=51), baseline IGA scores ranged from mild disease to severe disease, with the most common category being severe disease (*n*=36; 70.6%) across all stratifications (see Table 1Table 4).

Table 4 IGA scores at baseline

			Stratification						
			Age group			**Immunosuppressant use at enrolment**		**Gender**	
Statistic	**Measure**	**All** (*n*=51)	**Younger Adults** (*n*=12)	**Middle-aged Adults** (*n*=17)	**Older Adults** (*n*=21)	**No** (*n*=25)	**Yes** (*n*=26)	**Female** (*n*=17)	**Male** (*n*=34)
Frequency (n, % within stratification group)	**IGA scores 'clear' at baseline**	0	0	0	0	0	0	0	0
	IGA scores 'almost clear' at baseline	0	0	0	0	0	0	0	0

	IGA scores 'mild' at baseline	2 (3.9%)	0	1 95.9%)	1 (4.8%)	1 (4.0%)	1 (3.8%)	1 (5.9%)	1 (2.9%)
	IGA scores 'moderate' at baseline	13 (25.5%)	2 (16.7%)	5 (29.4%)	6 (28.6%)	6 (24.0%)	7 (26.9%)	5 (29.4%)	8 (23.5%)
	IGA scores 'severe' at baseline	36 (70.6%)	10 (83.3%)	11 (64.7%)	14 (66.7%)	18 (72.0%)	18 (69.2%)	11 (64.7%)	25 (73.5%)

Note: Age was not reported for one patient.

5.2.4. *DLQI scores at baseline*

DLQI baseline scores were not reported for 3 members of the follow-up sample. For the remaining sample (n=54), baseline EASI scores ranged from 3 (small impact) to 30 (extremely large impact), with both the most common category being a very large impact, and the sample mean values for the full cohort (18.26, SD = 6.18) and most stratifications (see Table 5) corresponding to a rating of a very large impact on the patient's life.

Table 5 DLQI scores at baseline

		Stratification							
			Age group			**Immunosuppressant use at enrolment**		**Gender**	
Statistic	**Measure**	**All** (*n*=54)	**Younger Adults** (*n*=14)	**Middle-aged Adults** (*n*=18)	**Older Adults** (*n*=21)	**No** (*n*=25)	**Yes** (*n*=29)	**Female** (*n*=19)	**Male** (*n*=35)
Mean (SD)	**DLQI score at baseline**	18.26 (6.18	17.36 (7.04)	19.06 (5.55)	18.33 (6.41)	19.48 (7.50)	17.21 (4.64)	20.11 (5.13)	17.26 (6.53)
Frequency (n, % within stratification group)	**DLQI scores 'no impact' at baseline**	0	0	0	0	0	0	0	0
	DLQI scores 'small impact' at baseline	1 (1.9%)	1 (7.1%)	0	0	1 (4.0%)	0	0	1 (2.9%)
	DLQI scores 'moderate impact' at baseline	4 (7.4%)	0	1 (5.6%)	3 (14.3%)	3 (12.0%)	1 (3.4%)	0	4 (11.4%)
	DLQI scores 'very large impact' at baseline	29 (53.7%)	9 (64.3%)	10 (55.6%)	9 (42.9%)	9 (36.0%)	20 (69.0%)	9 (47.4%)	20 (57.1%)
	DLQI scores 'extremely large impact' at baseline	20 (37.0%)	4 (28.6%)	7 (38.9%)	9 (42.9%)	12 (48.0%)	8 (27.6%)	10 (52.6%)	10 (28.6%)

Note: Age was not reported for one patient.

5.3. Main results

Please note, further descriptive statistics for all continuous variables are available in Table A1 in Appendix A.

5.3.1. *Change in EASI severity at the 16$^{+/-4}$ week follow-up*

16$^{+/-4}$ week follow-up EASI scores were available for a total of 32 patients and full stratified results are reported in Table 6.

The mean EASI score was 7.62 (SD = 6.26; range = 0.0 to 21.6), at the lower end of the 'moderate disease' category. Indeed, scores for half of patients for whom data were available at this time point correspond to ratings of 'moderate disease'. No patients were rated as having very severe disease, and only one had a score that would be categorised as severe disease.

Of the patients with a 16$^{+/-4}$ week follow-up EASI score, 2 did not have baseline EASI scores reported, thus the comparison sample totaled 30 patients. The mean change in EASI score was an improvement of 14.13 points (SD= 10.71; range = increased severity of 9.10 points to improvement of 33.10 points), or 55.84% (SD= 43.01%; range = increased severity by 79.82% to improvement of 100%) between baseline and the follow-up 16$^{+/-4}$ weeks from the first injection. In total, 20 patients (66.7%) showed a reduction of 50% or more from their baseline EASI score, with 22 patients (73.3%) reporting a reduction of at least 6.6 points, indicative of a minimally clinically important difference.

An unplanned inferential analysis was conducted to assess whether the magnitude of the difference between baseline and follow-up was statistically significant.

A paired-samples t-test indicated that the EASI scores at the 16$^{+/-4}$ week follow-up (mean 21.97) were significantly lower than at baseline (mean 7.84; $t(29)=7.226$, $p<0.001$).

Table 6 EASI scores at the 16$^{+/-4}$ week follow-up

		Stratification							
			Age group			**Immunosuppressant use at enrolment**		**Gender**	
		All (*n*=32)	**Younger Adults** (*n*=7)	**Middle-aged Adults** (*n*=13)	**Older Adults** (*n*=10)	**No** (*n*=11)	**Yes** (*n*=21)	**Female** (*n*=13)	**Male** (*n*=18)
EASI rating at the 16$^{+/-4}$ week follow-up									
Mean (SD)	**EASI score**	7.62 (6.26)	5.80 (6.16)	5.75 (4.15)	10.57 (8.05)	6.09 (6.73)	8.42 (6.02)	7.59 (6.16)	7.59 (6.69)
Frequency (n, % within stratification group)	**Clear**	5 (15.6%)	2 (28.6%)	2 (15.4%)	1 (10.0%)	3 (27.3%)	2 (9.5%)	3 (23.1%)	2 (11.1%)
	Almost clear	1 (3.1%)	0	1 (7.7%)	0	1 (9.1%)	0	0	1 (5.6%)
	Mild	9 (28.1%)	2 (28.6%)	4 (30.8%)	3 (30.0%)	3 (27.3%)	6 (28.6%)	3 (23.1%)	6 (33.3%)
	Moderate	16 (50.0%)	3 (42.9%)	6 (46.2%)	5 (50.0%)	4 (36.4%)	12 (57.1%)	7 (53.8%)	4 (44.4%)
	Severe	1 (3.1%)	0	0	1 (10.0%)	0	1 (4.8%)	0	1 (5.6%)
	Very severe	0	0	0	0	0	0	0	0
Change in EASI severity between baseline and the 16$^{+/-4}$ week follow-up									
		All	**Younger**	**Middle-**	**Older**	**No**	**Yes**	**Female**	**Male**

		(*n*=30)	**Adults** (*n*=7)	**aged Adults** (*n*=13)	**Adults** (*n*=9)	(*n*=11)	(*n*=19)	(*n*=12)	(*n*=18)
Mean (SD)	**Absolute change in EASI score**	14.13 (10.71)	12.24 (9.90)	13.38 (10.93)	15.59 (11.85)	16.04 (12.08)	13.03 (10.01)	11.36 (9.90)	15.98 (11.10)
	Percentage change in EASI score	55.84% (43.01%)	64.92% (31.75%)	55.91% (44.29%)	47.71% (53.40%)	62.46% (53.16%)	52.00% (36.98%)	51.69% (40.63%)	58.60% (45.46%)
Frequency (n, % within stratification group)	**MCID reduction**	22 (73.3%)	5 (71.4%)	9 (69.2%)	7 (77.8%)	8 (72.7%)	14 (73.7%)	8 (66.7%)	14 (77.8%)
	50% reduction or greater	20 (66.7%)	3 (42.9%)	10 (76.9%)	6 (66.7%)	9 (81.8%)	11 (57.9%)	8 (66.7%)	12 (66.7%)
	75% reduction or greater	11 (36.7%)	3 (42.9%)	5 (38.5%)	3 (33.3%)	6 (54.5%)	5 (26.3%)	3 (25.0%)	8 (44.4%)

Note: Age was not reported for two patients, and gender for one patient, for whom 16+/-4 week EASI scores were available. Age was not reported for one patient for whom change scores were available.

5.3.2. *Change in IGA severity at the 16$^{+/-4}$ week follow-up*

16$^{+/-4}$ week follow-up IGA scores were available for a total of 34 patients and full and stratified results are reported in Table 7. At the 16$^{+/-4}$ week follow-up, the IGA scores for the more than half of patients for whom data were available were rated as clear (17.6%) or almost clear (41.2%). Only one patient (2.9%) had a rating of severe disease.

Both baseline and 16$^{+/-4}$ week follow-up IGA scores were available for a total of 28 patients. Assessment of the direction of change demonstrated that for 21 (75%) patients, the IGA ratings improved by two or more categories, and a further 5 (17.9%) demonstrated an improvement of one category. For one patient there was no recorded change from baseline, and the IGA rating increased in severity for the one remaining patient.

An unplanned inferential analysis was conducted to assess whether the magnitude of the difference between baseline and follow-up was statistically significant. A Wilcoxon Signed Ranks test indicated that the IGA scores at the 16$^{+/-4}$ week follow-up (median = 1) were significantly lower than at baseline (median = 4; Z=-4.50, p<0.001).

Table 7 IGA scores at the 16$^{+/-4}$ week follow-up

		Stratification							
		All (*n*=34)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=6)	**Middle-aged Adults** (*n*=13)	**Older Adults** (*n*=14)	**No** (*n*=14)	**Yes** (*n*=20)	**Female** (*n*=11)	**Male** (*n*=22)
% within stratification	**IGA rating at the 16$^{+/-4}$ week follow-up**								
	Clear	6 (17.6%)	2 (33.3%)	2 (15.4%)	2 (14.3%)	4 (28.6%)	2 (10.0%)	3 (27.3%)	3 (13.6%)

	Almost clear	14 (41.2%)	2 (33.3%)	5 (38.5%)	7 (50.0%)	6 (42.9%)	8 (40.0%)	2 (18.2%)	12 (54.5%)
	Mild disease	9 (26.5%)	2 (33.3%)	4 (30.8%)	2 (14.3%)	2 (14.3%)	7 (35.0%)	4 (36.4%)	4 (18.2%)
	Moderate disease	4 (11.8%)	0	2 (15.4%)	2 (14.3%)	1 (7.1%)	3 (15.0%)	2 (18.2%)	2 (9.1%)
	Severe disease	1 (2.9%)	0	0	1 (7.1%)	1 (7.1%)	0	0	1 (4.5%)
	Change in IGA severity between baseline and the 16$^{+/-4}$ week follow-up								
		All (*n*=28)	**Younger Adults** (*n*=4)	**Middle-aged Adults** (*n*=12)	**Older Adults** (*n*=12)	**No** (*n*=13)	**Yes** (*n*=15)	**Female** (*n*=8)	**Male** (*n*=20)
	Increase in severity	1 (3.6%)	0	1 (8.3%)	0	0	1 (6.7%)	1 (12.5%)	0
	No change in severity	1 (3.6%)	0	0	1 (8.3%)	1 (7.7%)	0	0	1 (5.0%)
	Improvement by one category	5 (17.9%)	1 (25.0%)	2 (16.7%)	2 (16.7%)	2 (15.4%)	3 (20.0%)	2 (25.0%)	3 (15.0%)
	Improvement by two or more categories	21 (75.0%)	3 (75.0%)	9 (75.0%)	9 (75.0%)	10 (76.9%)	11 (73.3%)	5 (62.5%)	16 (80.0%)

Note: Age was not reported for one patient. Gender was not reported for one patient.

5.3.3. *Change in DLQI severity at the 16$^{+/-4}$ week follow-up*

16+/- 4 week follow-up DLQI scores were available for a total of 42 patients and the full and stratified results are reported in Table 8. The mean DLQI score was 7.86 (SD = 9.49; range = 0 to 39), at the lower end of the 'moderate impact' category. More than half of patients for whom data were available at this time point reported scored corresponding to small (21.4%) or no (33.3%) impact.

Of the patients with a 16$^{+/-4}$ week follow-up DLQI score, 2 did not have baseline DLQI scores reported, thus the comparison sample totaled 40 patients. The mean change in DLQI score was an improvement of 8.98 points (SD= 7.91; range = increased impact of 14 points to a reduced impact of 29 points), or 58.85% (SD= 42.11%; range = increased impact by 56% to reduced impact of 100%) between baseline and the follow-up 16+/-4 weeks from the first injection. In total, 32 patients (80.0%) reported a reduction of at least 4 points, indicative of a minimally clinically important difference. Of the 30 patients for whom both EASI and DLQI change scores were available at the 16$^{+/-4}$ week follow-up, 16 (53.3%) reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

An unplanned inferential analysis was conducted to assess whether the magnitude of the difference between baseline and follow-up was statistically significant.

A paired-samples t-test indicated that the DLQI scores at the 16$^{+/-4}$ week follow-up (mean 8.09) were significantly lower than at baseline (mean 17.05; t(39)=7.175, p<0.001).

Table 8 DLQI scores at the 16$^{+/-4}$ week follow-up

Stratification			
All (*n*=42)	**Age group**	**Immunosuppressant use at enrolment**	**Gender**

			Younger Adults (*n*=8)	Middle-aged Adults (*n*=16)	Older Adults (*n*=16)	No (*n*=16)	Yes (*n*=26)	Female (*n*=14)	Male (*n*=27)
DLQI rating at the 16$^{+/-4}$ week follow-up									
Mean (SD)	**DLQI score**	7.86 (9.49)	7.13 (8.34)	10.06 (11.33)	6.12 (8.75)	4.44 (7.08)	9.96 (10.27)	8.57 (9.25)	7.52 (9.94)
Frequency (n, % within stratification group)	**No impact**	14 (33.3%)	3 (37.5%)	4 (25.0%)	7 (43.8%)	8 (50.0%)	6 (32.1%)	5 (35.7%)	9 (33.3%)
	Small impact	9 (21.4%)	2 (25.0%)	3 (18.8%)	4 (25.0%)	4 (25.0%)	5 (19.2%)	1 (7.1%)	8 (29.6%)
	Moderate impact	7 (16.7%)	0	4 (25.0%)	1 (6.3%)	2 (12.5%)	5 (19.2%)	3 (21.4%)	3 (11.1%)
	Very large impact	6 (14.3%)	2 (25.0%)	2 (12.5%)	2 (12.5%)	0	6 (23.1%)	3 (21.4%)	3 (11.1%)
	Extremely large impact	6 (14.3%)	1 (12.5%)	3 (18.8%)	2 (12.5%)	2 (12.5%)	4 (15.4%)	2 (14.3%)	4 (14.8%)
Change in DLQI severity between baseline and the 16$^{+/-4}$ week follow-up									
		All (*n*=40)	**Younger Adults** (*n*=8)	**Middle-aged Adults** (*n*=16)	**Older Adults** (*n*=15)	**No** (*n*=16)	**Yes** (*n*=24)	**Female** (*n*=13)	**Male** (*n*=27)
Mean (SD)	**Absolute change in DLQI score**	8.98 (7.91)	9.38 (4.69)	8.38 (10.65)	9.47 (6.41)	12.13 (7.97)	6.88 (7.30)	10.54 (9.23)	8.22 (7.26)
	Percentage change in DLQI score	58.85% (42.11%)	67.13% (33.22%)	47.80% (48.99%)	66.60% (39.65%)	75.90% (34.34%)	47.48% (43.60%)	54.64% (44.31%)	60.88% (41.73%)
Frequency (n, % within stratification group)	**MCID reduction**	32 (80.0%)	7 (87.5%)	11 (68.8%)	13 (86.7%)	14 (87.5%)	18 (75.0%)	10 (76.9%)	22 (81.5%)
		All (*n*=30)	**Younger Adults** (*n*=7)	**Middle-aged Adults** (*n*=13)	**Older Adults** (*n*=9)	**No** (*n*=11)	**Yes** (*n*=19)	**Female** (*n*=12)	**Male** (*n*=18)
	DLQI MCID and EASI 50% reduction or greater	16 (53.3%)	2 (28.6%)	7 (53.9%)	6 (66.7%)	8 (72.7%)	8 (42.1%)	7 (58.3%)	9 (50.0%)

Note: Age was not reported for two patients, and gender for one patient, for whom 16+/-4 week DLQI scores were available. Age was not reported for one patient for whom change scores were available.

5.3.4. *Clinician-rated response to treatment at the 16$^{+/-4}$ week follow-up*

The most common clinician-rated treatment response for the 26 patients for whom data were available at the 16$^{+/-4}$ week follow-up was 'much better'. Two patients, both middle-aged and using immunosuppressants at the time of enrolment, were rated as having worse signs and symptoms, while a further two were rated as showing no change. Full and stratified results are reported in Table 9.

Table 9 Clinician-rated response to treatment at the 16$^{+/-4}$ week follow-up

		Stratification							
		All (*n*=26)	Age group			Immunosuppressant use at enrolment		Gender	
			Younger Adults (*n*=4)	Middle-aged Adults (*n*=10)	Older Adults (*n*=11)	No (*n*=9)	Yes (*n*=17)	Female (*n*=7)	Male (*n*=19)
Clinician rated response to treatment at the 16$^{+/-4}$ week follow-up									
Frequency (n, % within stratification group)	**Much worse**	0	0	0	0	0	0	0	0
	Worse	2 (7.7%)	0	2 (20.0%)	0	0	2 (11.8%)	1 (14.3%)	1 (5.3%)
	About the same	2 (7.7%)	0	1 (10.0%)	0	0	2 (11.8%)	2 (28.6%)	0
	Somewhat better	5 (19.2%)	2 (50.0%)	0	3 (27.3%)	0	5 (29.4%)	1 (14.3%)	4 (21.1%)
	Much better	17 (65.4%)	2 (50.0%)	7 (70.0%)	8 (72.7%)	9 (100%)	8 (47.1%)	3 (42.9%)	14 (73.7%)

Note: Age was not reported for one patient for whom 16$^{+/-4}$ week clinician-rated treatment response scores were available.

5.3.5. *Relationships between endpoints at the 16$^{+/-4}$ week follow-up*

Pearson's correlations were used to assess the strength and direction of any relationships between the endpoints and are reported fully in Table 10. Positive relationships between severity scales were significant and considered moderate to strong, particularly between the EASI and the IGA. Similarly, disease severity was negatively correlated to clinician-rated treatment response, although these relationships were less strong and adopting a Bonferroni-corrected alpha of $p<0.008$ to account for the multiple comparisons, the relationship between clinician-rated response and EASI scores did not meet significance.

Table 10 Correlations between severity scores at the 16$^{+/-4}$ week follow-up

Measure	EASI at the 16$^{+/-4}$ week follow-up	IGA at the 16$^{+/-4}$ week follow-up	DLQI at the 16$^{+/-4}$ week follow-up	Clinician-rated response at the 16$^{+/-4}$ week follow-up
EASI at the 16$^{+/-4}$ week follow-up				
IGA at the 16$^{+/-4}$ week follow-up	0.89 ($p<0.001$; $n=24$)			
DLQI at the 16$^{+/-4}$ week follow-up	0.67 ($p<0.001$; $n=32$)	0.75 ($p<0.001$; $n=34$)		
Clinician-rated response at the 16$^{+/-4}$ week follow-up	-0.47 ($p=0.51$; $n=18$)	-0.66 ($p=0.003$; $n=18$)	-0.64 ($p=0.001$; $n=25$)	

5.4. Other analyses

5.4.1. *Change in EASI severity at all other follow-ups*

2 to 4 week follow-up EASI scores were available for a total of 16 patients and full stratified results are reported in Table 11. The mean EASI score was 7.98 (SD = 13.45; range = 0.0 to 54.0), at the lower end of the 'moderate disease' category. Scores for around 70% of patients for whom data were available at this time point corresponded to ratings of clear (18.8%), almost clear (12.5%) or mild disease (37.5%). No patients were rated as having severe disease, and only one had a score that would be categorised as very severe disease.

For all 16 patients, a baseline EASI score was also available. The mean change in EASI score was an improvement of 18.87 points (SD= 15.74; range = improvement of 3.2 points to 53.9 points), or 68.33% (SD= 31.12%; range = improvement of 17.92% to 100%) between baseline and the follow-up 2 to 4 weeks from the first injection. In total, 11 patients (68.8%) showed a reduction of 50% or more from their baseline EASI score, with 5 patients (31.3%) reporting a reduction of at least 6.6 points, indicative of a minimally clinically important difference.

Table 11 EASI scores at the 2 to 4 week follow-up

		Stratification							
		All (*n*=16)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=3)	**Middle-aged Adults** (*n*=6)	**Older Adults** (*n*=7)	**No** (*n*=11)	**Yes** (*n*=5)	**Female** (*n*=8)	**Male** (*n*=8)
EASI rating at the 2 to 4 week follow-up									
Mean (SD)	**EASI score**	7.98 (13.45)	8.37 (8.14)	6.35 (5.92)	9.20 (19.91)	7.65 (15.66)	8.68 (7.99)	5.20 (6.14)	10.75 (18.23)
Frequency (n, % within stratification group)	**Clear**	3 (18.8%)	0	1 (16.7%)	2 (28.6%)	3 (27.3%)	0	3 (37.5%)	0
	Almost clear	2 (12.5%)	0	0	2 (28.6%)	1 (9.1%)	1 (20.0%)	0	2 (25.0%)
	Mild	6 (37.5%)	2 (66.7%)	2 (33.3%)	2 (28.6%)	5 (45.5%)	1 (20.0%)	2 (25.0%)	4 (50.0%)
	Moderate	4 (25.0%)	1 (33.3%)	3 (50.0%)	0	1 (9.1%)	3 (60.0%)	3 (37.5%)	1 (12.5%)
	Severe	0	0	0	0	0	0	0	0
	Very severe	1 (6.3%)	0	0	1 (14.3%)	1 (9.1%)	0	0	1 (12.5%)
Change in EASI severity between baseline and the 2 to 4 week follow-up									
		All (*n*=16)	**Younger Adults** (*n*=3)	**Middle-aged Adults** (*n*=6)	**Older Adults** (*n*=7)	**No** (*n*=11)	**Yes** (*n*=5)	**Female** (*n*=8)	**Male** (*n*=8)
Mean (SD)	**Absolute change in EASI score**	18.87 (15.74)	20.33 (29.07)	14.18 (12.96)	22.26 (12.70)	22.46 (15.71)	10.96 (14.07)	19.39 (18.20)	18.35 (14.11)
	Percentage change in EASI score	68.33% (31.12%)	58.37% (36.79%)	63.24% (30.94%)	76.97% (31.77%)	76.83% (27.43%)	49.65% (33.39%)	70.22% (34.47%)	66.45% (29.65%)

Frequency (n, % within stratification group)	**MCID reduction**	5 (31.3%)	2 (66.7%)	2 (33.3%)	1 (14.3%)	2 (18.2%)	3 (60.0%)	3 (37.5%)	2 (25.0%)
	50% reduction or greater	11 (68.8%)	1 (33.3%)	4 (66.7%)	6 (85.7%)	9 (81.8%)	2 (40.0%)	5 (62.5%)	6 (75.0%)
	75% reduction or greater	9 (56.3%)	1 (33.3%)	3 (50.0%)	5 (71.4%)	8 (72.7%)	1 (20.0%)	5 (62.5%)	4 (50.0%)

4 to 8 week follow-up EASI scores were available for a total of 19 patients and the full and stratified results are reported in Table 12. The mean EASI score was 9.57 (SD = 10.42; range = 0.0 to 35.0), in the 'moderate disease' category, though the most common rating was of mild disease (52.6%). No patients had a score that would be categorised as very severe disease.

A baseline EASI score was also available for 17 of the patients with a 4 to 8 week follow-up score. The mean change in EASI score was an improvement of 16.46 points (SD= 12.81; range = increased severity of 4.6 points to an improvement of 40.50 points), or 60.25% (SD= 36.94%; range = increased severity of 16.79% to an improvement of 100%) between baseline and the follow-up 4 to 8 weeks from the first injection. In total, 12 patients (70.6%) showed a reduction of 50% or more from their baseline EASI score, with 13 patients (76.5%) reporting a reduction of at least 6.6 points, indicative of a minimally clinically important difference.

Table 12 EASI scores at the 4 to 8 week follow-up

		Stratification							
		All (*n*=19)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=6)	**Middle-aged Adults** (*n*=4)	**Older Adults** (*n*=7)	**No** (*n*=9)	**Yes** (*n*=10)	**Female** (*n*=7)	**Male** (*n*=11)
EASI rating at the 4 to 8 week follow-up									
Mean (SD)	**EASI score**	9.57 (10.42)	11.77 (11.02)	2.57 (2.06)	11.66 (13.29)	10.39 (13.42)	8.84 (7.48)	8.11 (8.58)	10.77 (12.14)
Frequency (n, % within stratification group)	**Clear**	2 (10.5)	0	1 (25.0%)	1 (14.3%)	2 (22.2%)	0	1 (14.3%)	1 (9.1%)
	Almost clear	0	0	0	0	0	0	0	0
	Mild	10 (52.6%)	4 (66.7%)	3 (75.0%)	2 (28.6%)	4 (44.4%)	6 (60.0%)	3 (42.9%)	6 (54.5%)
	Moderate	4 (21.1%)	1 (16.7%)	0	2 (28.6%)	1 (11.1%)	3 (30.0%)	2 (28.6%)	2 (18.2%)
	Severe	3 (15.8%)	1 (16.7%)	0	2 (28.6%)	2 (22.2%)	1 (10.0%)	1 (14.3%)	2 (18.2%)
	Very severe	0	0	0	0	0	0	0	0
Change in EASI severity between baseline and the 4 to 8 week follow-up									
		All (*n*=17)	**Younger Adults**	**Middle-aged**	**Older Adults**	**No** (*n*=9)	**Yes** (*n*=8)	**Female** (*n*=6)	**Male** (*n*=11)

			(*n*=6)	**Adults** (*n*=4)	(*n*=6)				
Mean (SD)	**Absolute change in EASI score**	16.46 (12.82)	10.42 (10.25)	15.98 (9.63)	21.05 (16.52)	18.50 (11.00)	14.18 (15.03)	18.00 (10.64)	15.63 (14.29)
	Percentage change in EASI score	60.25% (36.94%)	47.65% (44.05%)	78.98% (22.87%)	21.05% (16.52%)	69.48% (35.85%)	49.88% (37.65%)	65.95% (38.65%)	57.14% (37.50%)
Frequency (n, % within stratification group)	**MCID reduction**	13 (76.5%)	4 (66.7%)	3 (75.0%)	5 (83.3%)	8 (88.9%)	5 (62.5%)	5 (83.3%)	8 (72.7%)
	50% reduction or greater	12 (70.6%)	4 (66.7%)	3 (75.0%)	4 (66.7%)	8 (88.9%)	4 (50.0%)	5 (83.3%)	7 (63.6%)
	75% reduction or greater	7 (41.2%)	2 (33.3%)	3 (75.0%)	2 (33.3%)	5 (55.6%)	2 (25.0%)	3 (50.0%)	4 (36.4%)

Note: Age was not reported for two patients, and gender for one patient, for whom 4 to 8 week EASI scores were available. Age was not reported for one patient for whom change scores were available.

8 to 12 week follow-up EASI scores were available for a total of 12 patients and the full and stratified results are reported in Table 13. The mean EASI score was 10.78 (SD = 11.74; range = 0.0 to 40.2), in the 'moderate disease' category, which was also most common rating was of mild disease (41.7%). No patients had a score that would be categorised as very severe disease.

A baseline EASI score was also available for all 12 of the patients with an 8 to 12 week follow-up score. The mean change in EASI score was an improvement of 23.71 points (SD= 13.32; range = an improvement of 4.30 points to 57.90 points), or 71.63% (SD= 25.30%; range = an improvement of 16.93% to 100%) between baseline and the follow-up 8 to 12 weeks from the first injection. In total, 9 patients (75.0%) showed a reduction of 50% or more from their baseline EASI score, with 11 patients (91.7%) reporting a reduction of at least 6.6 points, indicative of a minimally clinically important difference.

Table 13 EASI scores at the 8 to 12 week follow-up

		Stratification							
		All (*n*=12)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=7)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=4)	**No** (*n*=5)	**Yes** (*n*=7)	**Female** (*n*=2)	**Male** (*n*=10)
EASI rating at the 8 to 12 week follow-up									
Mean (SD)	**EASI score**	10.78 (11.74)	6.14 (7.47)	12.90 (*n/a*)	18.38 (16.28)	11.18 (16.62)	10.50 (8.26)	1.05 (1.48)	12/73 (11.95)
Frequency (n, % within stratification group)	**Clear**	2 (16.7%)	2 (28.6%)	0	0	1 (20.0%)	1 (14.3%)	1 (50.0%)	1 (10.0%)
	Almost clear	0	0	0	0	0	0	0	0

	Mild	3 (25.0%)	2 (28.6%)	0	1 (25.0%)	2 (40.0%)	1 (14.3%)	1 (50.0%)	2 (20.0%)
	Moderate	5 (41.7%)	3 (42.9%)	1 (100%)	1 (25.0%)	1 (20.0%)	4 (14.3%)	0	5 (50.0%)
	Severe	2 (16.7%)	0	0	2 (50.0%)	1 (20.0%)	1 (14.3%)	0	2 (20.0%)
	Very severe	0	0	0	0	0	0	0	0
Change in EASI severity between baseline and the 8 to 12 week follow-up									
		All (*n*=12)	**Younger Adults** (*n*=7)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=4)	**No** (*n*=5)	**Yes** (*n*=7)	**Female** (*n*=2)	**Male** (*n*=10)
Mean (SD)	**Absolute change in EASI score**	23.71 (13.32)	24.64 (15.59)	28.90 (*n/a*)	20.78 (11.91)	32.20 (15.24)	17.64 (8.22)	33.55 (34.44)	21.74 (7.70)
	Percentage change in EASI score	71.63% (25.30%)	81.57% (19.81%)	69.14% (*n/a*)	54.86% (30.89%)	78.49% (23.63%)	66.73% (27.09%)	98.25% (2.57%)	66.31% (24.34%)
Frequency (n, % within stratification group)	**MCID reduction**	11 (91.7%)	7 (100%)	1 (100%)	3 (75.0%)	5 (100%)	6 (85.7%)	2 (100%)	9 (90.0%)
	50% reduction or greater	9 (75.0%)	6 (85.7%)	1 (100%)	2 (50.0%)	4 (80.0%)	5 (71.4%)	2 (100%)	7 (70.0%)
	75% reduction or greater	5 (41.7%)	4 (33.3%)	0	1 (25.0%)	3 (60.0%)	2 (28.6%)	2 (100%)	3 (30.0%)

20 or more week follow-up EASI scores were available for a total of 8 patients and full and stratified results are reported in Table 14. The mean EASI score was 4.40 (SD = 3.76; range = 0.5 to 12.0), in the 'mild disease' category, which was also most common rating (50.0%). No patients had a score that would be categorised as clear, severe or very severe disease.

Both baseline and 20 or more week follow-up EASI scores were available for 7 patients. The mean change in EASI score was an improvement of 16.44 points (SD= 11.89; range = an improvement of 2.00 points to 31.50 points), or 72.99% (SD= 25.82%; range = an improvement of 21.74% to 97.75%) between baseline and the follow-up 8 to 12 weeks from the first injection. In total, 6 patients (85.7%) showed a reduction of 50% or more from their baseline EASI score, with 5 patients (71.4%) reporting a reduction of at least 6.6 points, indicative of a minimally clinically important difference.

Table 14 EASI scores at the 20 or more week follow-up

	Stratification						
	All (*n*=8)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**
		Younger Adults (*n*=4)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=2)	**No** (*n*=2)	**Yes** (*n*=6)	**Female** (*n*=3)	**Male** (*n*=4)
EASI rating at the 20 or more week follow-up							

Mean (SD)	**EASI score**	4.40 (3.76)	6.38 (4.33)	0.50 (*n/a*)	2.55 (2.19)	2.55 (2.19)	5.02 (4.12)	4.03 (3.37)	4.75 (5.01)
Frequency (n, % within stratification group)	**Clear**	0	0	0	0	0	0	0	0
	Almost clear	2 (25.0%)	0	1 (100%)	1 (50.0%)	1 (50.0%)	1 (16.7%)	1 (33.3%)	1 (25.0%)
	Mild	4 (50.0%)	2 (50.0%)	0	1 (50.0%)	1 (50.0%)	3 (50.0%)	1 (33.3%)	2 (50.0%)
	Moderate	2 (25.0%)	2 (50.0%)	0	0	0	2 (33.3%)	1 (33.3%)	1 (25.0%)
	Severe	0	0	0	0	0	0	0	0
	Very severe	0	0	0	0	0	0	0	0
Change in EASI severity between baseline and the 20 or more week follow-up									
		All (*n*=7)	**Younger Adults** (*n*=4)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=2)	**No** (*n*=2)	**Yes** (*n*=5)	**Female** (*n*=3)	**Male** (*n*=4)
Mean (SD)	**Absolute change in EASI score**	16.44 (11.89)	12.83 (13.01)	21.70 (*n/a*)	21.05 (14.78)	21.05 (14.78)	14.60 (11.94)	13.50 (10.26)	18.65 (14.05)
	Percentage change in EASI score	72.99% (25.82%)	58.31% (25.48%)	97.75% (*n/a*)	89.93% (2.05%)	89.93% (2.05%)	66.21% (28.24%)	66.24% (39.64%)	78.04% (14.35%)
Frequency (n, % within stratification group)	**MCID reduction**	5 (71.4%)	2 (50.0%)	1 (100%)	2 (100%)	2 (100%)	3 (60.0%)	2 (66.7%)	3 (75.0%)
	50% reduction or greater	6 (85.7%)	3 (75.0%)	1 (100%)	2 (100%)	2 (100%)	4 (80.0%)	2 (66.7%)	4 (100%)
	75% reduction or greater	4 (57.1%)	1 (25.0%)	1 (100%)	2 (100%)	2 (100%)	2 (40.0%)	2 (66.7%)	2 (50.0%)

Note: Age was not reported for one patient for whom 20 or more week follow-up EASI scores were available.

5.4.2. *Change in IGA severity at all other follow-ups*

2 to 4 week follow-up IGA scores were available for a total of 21 patients. Both baseline and 2 to 4 week follow-up IGA scores were available for a total of 20 patients. Full and stratified results are reported in Table 15.

At the 2 to 4 week follow-up, no patients for whom data were available were rated as having severe disease, with over one third having IGA ratings of clear (9.5%) or almost clear (28.6%), with a further 38.1% rated as having mild disease. This is reflected in the difference scores, which show that in the period between baseline and the 2 to 4 week follow-up from first injection, 95% patients were reported as having a reduction in AD severity of at least one IGA category, with the majority (55%) improving by at least two categories. Only one patient for whom data was available was reported as showing no change from baseline and no patients were reported to show an increase in severity.

Table 15 IGA scores at the 2 to 4 week follow-up

		Stratification							
		All (*n*=21)	Age group			Immunosuppressant use at enrolment		Gender	
			Younger Adults (*n*=3)	Middle-aged Adults (*n*=8)	Older Adults (*n*=10)	No (*n*=11)	Yes (*n*=10)	Female (*n*=8)	Male (*n*=13)
Frequency (n, % within stratification group)	**IGA rating at the 2 to 4 week follow-up**								
	Clear	2 (9.5%)	0	1 (12.5%)	1 (10.0%)	2 (18.2%)	0	2 (25.0%)	0
	Almost clear	6 (28.6%)	2 (66.7%)	1 (12.5%)	3 (30.0%)	3 (27.3%)	3 (30.0%)	1 (12.5%)	5 (38.5%)
	Mild disease	8 (38.1%)	1 (33.3%)	2 (25.0%)	5 (50.0%)	5 (45.5%)	3 (30.0%)	3 (37.5%)	5 (38.5%)
	Moderate disease	5 (23.8%)	0	4 (50.0%)	1 (10.0%)	1 (9.1%)	4 (40.0%)	2 (25.0%)	3 (23.1%)
	Severe disease	0	0	0	0	0	0	0	0
	Change in IGA severity between baseline and the 2 to 4 week follow-up								
		All (*n*=21)	**Younger Adults** (*n*=2)	**Middle-aged Adults** (*n*=8)	**Older Adults** (*n*=10)	**No** (*n*=11)	**Yes** (*n*=9)	**Female** (*n*=8)	**Male** (*n*=12)
	Increase in severity	0	0	0	0	0	0	0	0
	No change in severity	1 (5.0%)	0	0	1 (10.0%)	1 (9.1%)	0	0	1 (8.3%)
	Improvement by one category	8 (40.0%)	1 (50.0%)	4 (50.0%)	3 (30.0%)	2 (18.2%)	6 (66.7%)	5 (62.5%)	3 (25.0%)
	Improvement by two or more categories	11 (55.0%)	1 (50.0%)	4 (50.0%)	6 (60.0%)	8 (72.7%)	3 (33.3%)	3 (37.5%)	8 (66.7%)

4 to 8 week follow-up IGA scores were available for a total of 17 patients. Both baseline and 2 to 4 week follow-up IGA scores were available for a total of 15 patients. Full and stratified results are reported in Table 16.

At the 4 to 8 week follow-up, as at the first follow-up, no patients for whom data were available were rated as having severe disease. Close to half of the sample were reported as having IGA ratings of clear (17.6%) or almost clear (29.4%). The most common IGA rating was mild disease (47.1%), with only one patient rated as having moderate disease (5.9%).

The difference scores, show a similar pattern of results in the 4 to 8 week follow-up as that observed in the period between baseline and the 2 to 4 week follow-up from first injection. The vast majority >90% patients were reported as having a reduction in AD severity of at least one IGA category, with around half (47%) improving by at least two categories. Only one patient for whom data was available was reported as showing no change from baseline and no patients were reported to show an increase in severity.

Table 16 IGA scores at the 4 to 8 week follow-up

	Stratification

		All (*n*=17)	Age group			Immunosuppressant use at enrolment		Gender	
			Younger Adults (*n*=4)	Middle-aged Adults (*n*=2)	Older Adults (*n*=10)	No (*n*=9)	Yes (*n*=8)	Female (*n*=7)	Male (*n*=9)
Frequency (n, % within stratification group)	**IGA rating at the 4 to 8 week follow-up**								
	Clear	3 (17.6%)	0	1 (50.0%)	2 (20.0%)	2 (22.2%)	1 (12.5%)	2 (28.6%)	1 (11.1%)
	Almost clear	5 (29.4%)	1 (25.0%)	1 (50.0%)	3 (30.0%)	4 (44.4%)	1 (12.5%)	2 (28.6%)	3 (33.3%)
	Mild disease	8 (47.1%)	3 (75.0%)	0	4 (40.0%)	2 (22.2%)	6 (75.0%)	2 (28.6%)	5 (55.6%)
	Moderate disease	1 (5.9%)	0	0	1 (10.0%)	1 (11.1%)	0	1 (14.3%)	0
	Severe disease	0	0	0	0	0	0	0	0
	Change in IGA severity between baseline and the 4 to 8 week follow-up								
		All (*n*=15)	**Younger Adults** (*n*=4)	**Middle-aged Adults** (*n*=2)	**Older Adults** (*n*=9)	**No** (*n*=9)	**Yes** (*n*=6)	**Female** (*n*=)	**Male** (*n*=)
	Increase in severity	0	0	0	0	0	0	0	0
	No change in severity	1 (6.7%)	0	0	1 (11.1%)	1 (11.1%)	0	1 (16.7%)	0
	Improvement by one category	7 (46.7%)	2 (50.0%)	0	5 (55.6%)	3 (33.3%)	4 (66.7%)	2 (33.3%)	5 (55.6%)
	Improvement by two or more categories	7 (46.7%)	2 (50.0%)	2 (100.0%)	3 (33.3%)	5 (55.6%)	2 (33.3%)	3 (50.0%)	4 (44.4%)

Note: Age was not reported for one patient for whom baseline IGA scores were available.

8 to 12 week follow-up IGA scores were available for a total of 14 patients. Both baseline and 8 to 12 week follow-up IGA scores were available for a total of 13 patients. Full and stratified results are reported in Table 17.

The data available for a follow-up 8 to 12 weeks from first injection demonstrates a similar pattern of results to the previous follow-ups. However, in this follow-up more than half of the sample were rated as having clear (14.3%) or almost clear (42.9%) IGA scores. This is reflected in the fact that difference scores indicate >90% the sample improved by two or more IGA categories.

Table 17 IGA scores at the 8 to 12 week follow-up

		Stratification							
		All (*n*=14)	Age group			Immunosuppressant use at enrolment		Gender	
			Younger Adults (*n*=6)	Middle-aged Adults (*n*=2)	Older Adults (*n*=6)	No (*n*=3)	Yes (*n*=11)	Female (*n*=1)	Male (*n*=13)
n	**IGA rating at the 8 to 12 week follow-up**								

	Clear	2 (14.3%)	2 (33.3%)	0	0	1 (33.3%)	1 (9.1%)	1 (100%)	1 (7.7%)
	Almost clear	6 (42.9%)	3 (50.0%)	0	3 (50.0%)	2 (66.7%)	4 (36.4%)	0	6 (46.2%)
	Mild disease	5 (35.7%)	1 (16.7%)	2 (100%)	2 (33.3%)	0	5 (45.5%)	0	5 (38.5%)
	Moderate disease	1 (7.1%)	0	0	1 (16.7%)	0	1 (9.1%)	0	1 (7.7%)
	Severe disease	0	0	0	0	0	0	0	0
	Change in IGA severity between baseline and the 8 to 12 week follow-up								
		All (*n*=13)	**Younger Adults** (*n*=5)	**Middle-aged Adults** (*n*=2)	**Older Adults** (*n*=6)	**No** (*n*=3)	**Yes** (*n*=10)	**Female** (*n*=0)	**Male** (*n*=13)
	Increase in severity	0	0	0	0	0	0	0	0
	No change in severity	0	0	0	0	0	0	0	0
	Improvement by one category	1 (7.7%)	0	0	1 (16.7%)	0	1 (10.0%)	0	1 (7.7%)
	Improvement by two or more categories	12 (92.3%)	5 (100%)	2 (100%)	5 (83.3%)	3 (100%)	9 (90.0%)	0	12 (92.3%)

20+ week follow-up IGA scores were available for a total of 10 patients. Both baseline and 20+ week follow-up IGA scores were available for a total of 6 patients. Full and stratified results are reported in Table 18.

Although the sample is very small, the results indicate that all patients for whom data were available had achieved an IGA rating of clear or almost clear, and that all had improved by two or more categories in the period between baseline and 20+ weeks from the first injection.

Table 18 IGA scores at the 20 or more week follow-up

		Stratification							
		All (*n*=10)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=5)	**Middle-aged Adults** (*n*=0)	**Older Adults** (*n*=4)	**No** (*n*=3)	**Yes** (*n*=7)	**Female** (*n*=2)	**Male** (*n*=7)
Frequency (n, % within stratification group)	**IGA rating at the 20 weeks or more follow-up**								
	Clear	7 (70.0%)	3 (60.0%)	0	3 (75.0%)	2 (66.7%)	5 (71.4%)	0	6 (85.7%)
	Almost clear	3 (30.0%)	2 (40.0%)	0	1 (25.0%)	1 (33.3%)	2 (28.6%)	2 (100%)	1 (14.3%)
	Mild disease	0	0	0	0	0	0	0	0

	Moderate disease	0	0	0	0	0	0	0	0
	Severe disease	0	0	0	0	0	0	0	0
	Change in IGA severity between baseline and the 20 weeks or more follow-up								
		All (*n*=6)	**Younger Adults** (*n*=3)	**Middle-aged Adults** (*n*=0)	**Older Adults** (*n*=3)	**No** (*n*=2)	**Yes** (*n*=4)	**Female** (*n*=1)	**Male** (*n*=5)
	Increase in severity	0	0	0	0	0	0	0	0
	No change in severity	0	0	0	0	0	0	0	0
	Improvement by one category	0	0	0	0	0	0	0	0
	Improvement by two or more categories	6 (100%)	3 (100%)	0	3 (100%)	2 (100%)	4 (100%)	1 (100%)	5 (100%)

Note: Age and gender were not reported for one patient for whom baseline data were available.

5.4.3. *Change in DLQI severity at all other follow-ups*

2 to 4 week follow-up DLQI scores were available for a total of 27 patients and full and stratified results are reported in Table 19.

The mean DLQI score was 6.07 (SD = 6.21; range = 0 to 25), at the lower end of the 'moderate impact' category. More than half of patients for whom data were available at this time point reported scored corresponding to small (18.5%) or no (37.0%) impact.

Of the patients with a 2 to 4 week follow-up DLQI score, 1 did not have baseline DLQI scores reported, thus the comparison sample totaled 26 patients. The mean change in DLQI score was an improvement of 13.15 points (SD= 7.96; range = no change to a reduced impact of 29 points), or 68.79% (SD= 30.05%; range = no change to reduced impact of 100%) between baseline and the follow-up 2 to 4 weeks from the first injection. In total, 24 patients (92.3%) reported a reduction of at least 4 points, indicative of a minimally clinically important difference. Of the 15 patients for whom both EASI and DLQI change scores were available at the 2 to 4 week follow-up, 9 (60.0%) reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

Table 19 DLQI scores at the 2 to 4 week follow-up

		Stratification							
		All (*n*=27)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=4)	**Middle-aged Adults** (*n*=9)	**Older Adults** (*n*=14)	**No** (*n*=16)	**Yes** (*n*=11)	**Female** (*n*=10)	**Male** (*n*=17)
DLQI rating at the 2 to 4 week follow-up									
Mean (SD)	**DLQI score**	6.07 (6.21)	8.00 (6.98)	7.67 (7.95)	4.50 (4.62)	4.69 (4.44)	8.09 (7.94)	6.00 (5.56)	6.12 (6.73)
within strati	**No impact**	10 (37.0%)	1 (25.0%)	2 (22.2%)	7 (50.0%)	7 (43.8%)	3 (27.3%)	3 (30.0%)	7 (41.2%)

	Small impact	5 (18.5%)	0	3 (33.3%)	2 (14.3%)	2 (12.5%)	3 (27.3%)	2 (20.0%)	3 (17.6%)
	Moderate impact	7 (25.9%)	2 (50.0%)	1 (11.1%)	4 (28.6%)	6 (37.5%)	1 (9.1%)	3 (30.0%)	4 (23.5%)
	Very large impact	4 (14.8%)	1 (25.0%)	2 (22.2%)	1 (7.1%)	1 (6.3%)	3 (27.3%)	2 (20.0%)	2 (11.8%)
	Extremely large impact	1 (3.7%)	0	1 (11.1%)	0	0	1 (9.1%)	0	1 (5.9%)
Change in DLQI severity between baseline and the 2 to 4 week follow-up									
		All (*n*=26)	**Younger Adults** (*n*=4)	**Middle-aged Adults** (*n*=9)	**Older Adults** (*n*=13)	**No** (*n*=15)	**Yes** (*n*=11)	**Female** (*n*=10)	**Male** (*n*=16)
Mean (SD)	**Absolute change in DLQI score**	13.15 (7.96)	11.25 (7.09)	12.11 (10.18)	14.46 (6.83)	16.33 (7.25)	8.82 (7.01)	14.70 (7.83)	12.19 (8.14)
	Percentage change in DLQI score	68.79% (30.05%)	60.99% (32.99%)	58.31% (38.19%)	78.45% (20.82%)	79.08% (19.65%)	54.77% (36.64%)	69.76% (27.07%)	68.19% (32.63%)
Frequency (n, % within stratification group)	**MCID reduction**	24 (92.3%)	4 (100%)	7 (77.8%)	13 (100%)	15 (100%)	9 (81.8%)	10 (100%)	14 (87.5%)
		All (*n*=15)	**Younger Adults** (*n*=3)	**Middle-aged Adults** (*n*=6)	**Older Adults** (*n*=6)	**No** (*n*=10)	**Yes** (*n*=5)	**Female** (*n*=8)	**Male** (*n*=7)
	DLQI MCID and EASI 50% reduction or greater	9 (60%)	2 (66.7%)	3 (50.0%)	4 (60.0%)	7 (70.0%)	2 (40.0%)	5 (62.5%)	4 (57.1%)

4 to 8 week follow-up DLQI scores were available for a total of 23 patients and full and stratified results are reported in Table 20. The mean DLQI score was 6.30 (SD = 6.68; range = 0 to 30), at the lower end of the 'moderate impact' category. More than half of patients for whom data were available at this time point reported scored corresponding to small (26.1%) or no (26.1%) impact.

Of the patients with a 4 to 8 week follow-up DLQI score, 2 did not have baseline DLQI scores reported, thus the comparison sample totaled 21 patients. The mean change in DLQI score was an improvement of 10.95 points (SD= 7.81; range = an increase in impact of 3 points to a reduced impact of 29 points), or 61.76% (SD= 34.44%; range = an increase in impact of 11.11% to reduced impact of 100%) between baseline and the follow-up 4 to 8 weeks from the first injection. In total, 17 patients (81.0%) reported a reduction of at least 4 points, indicative of a minimally clinically important difference. Of the 16 patients for whom both EASI and DLQI change scores were available at the 4 to 8 week follow-up, 9 (56.3%) reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

Table 20 DLQI scores at the 4 to 8 week follow-up

Stratification			
All (*n*=23)	**Age group**	**Immunosuppressant use at enrolment**	**Gender**

			Younger Adults (*n*=7)	Middle-aged Adults (*n*=4)	Older Adults (*n*=10)	No (*n*=12)	Yes (*n*=11)	Female (*n*=8)	Male (*n*=14)
DLQI rating at the 4 to 8 week follow-up									
Mean (SD)	**DLQI score**	6.30 (6.68)	10.71 (8.90)	3.50 (3.87)	3.40 (3.86)	6.33 (8.58)	6.27 (4.15)	5.38 (5.18)	6.79 (7.77)
Frequency (n, % within stratification group)	**No impact**	6 (26.1%)	0	1 (25.0%)	5 (50.0%)	5 (41.7%)	1 (9.1%)	2 (25.0%)	4 (28.6%)
	Small impact	6 (26.1%)	2 (28.6%)	2 (50.0%)	2 (20.0%)	2 (16.7%)	4 (36.4%)	3 (37.5%)	3 (21.4%)
	Moderate impact	8 (34.8%)	3 (42.9%)	1 (25.0%)	3 (30.0%)	3 (25.0%)	5 (45.5%)	2 (25.0%)	5 (35.7%)
	Very large impact	2 (8.7%)	1 (14.3%)	0	0	1 (8.3%)	1 (9.1%)	1 (12.5%)	1 (7.1%)
	Extremely large impact	1 (4.3%)	1 (14.3%)	0	0	1 (8.3%)	0	0	1 (7.1%)
Change in DLQI severity between baseline and the 4 to 8 week follow-up									
		All (*n*=21)	**Younger Adults** (*n*=7)	**Middle-aged Adults** (*n*=4)	**Older Adults** (*n*=9)	**No** (*n*=12)	**Yes** (*n*=9)	**Female** (*n*=7)	**Male** (*n*=14)
Mean (SD)	**Absolute change in DLQI score**	10.95 (7.81)	8.00 (6.11)	13.00 (9.76)	13.56 (7.52)	13.08 (9.15)	8.11 (4.65)	12.29 (6.52)	10.29 (8.53)
	Percentage change in DLQI score	61.76% (34.44%)	46.78% (28.34%)	67.68% (45.64%)	77.65% (24.62%)	67.27% (38.91%)	54.42% (27.87%)	66.53% (33.59%)	59.37% (35.85%)
Frequency (n, % within stratification group)	**MCID reduction**	17 (81.0%)	6 (85.7%)	3 (75.0%)	8 (88.9%)	10 (83.3%)	7 (77.8%)	6 (85.7%)	11 (78.6%)
		All (*n*=16)	**Younger Adults** (*n*=6)	**Middle-aged Adults** (*n*=4)	**Older Adults** (*n*=5)	**No** (*n*=9)	**Yes** (*n*=7)	**Female** (*n*=6)	**Male** (*n*=10)
	DLQI MCID and EASI 50% reduction or greater	9 (56.3%)	4 (66.7%)	2 (50.0%)	3 (60.0%)	7 (77.8%)	2 (28.6%)	4 (66.7%)	5 (50.0%)

Note: Age was not reported for two patients, and gender for one patient, for whom 4 to 8 week DLQI scores were available. Age was not reported for one patient for whom change scores were available.

8 to 12 week follow-up DLQI scores were available for a total of 17 patients and the full and stratified results are reported in Table 21. The mean DLQI score was 4.88 (SD = 6.00; range = 0 to 26), corresponding to a 'small impact' of AD on daily life, which is reflected by this category being the most common rating, applicable to almost half of patients (47.1%) for whom data at this follow-up were available.

All patients with 8 to 12 week follow-up DLQI scores also had baseline DLQI scores. The mean change in DLQI score was an improvement of 12.12 points (SD= 6.32; range = a reduced impact of 1 to 29 points), or 74.56% (SD= 22.41%; range = a reduced impact of 3.7% to 100%) between baseline and the follow-up 8 to 12 weeks from the first injection. In total, 15 patients (88.2%) reported a

reduction of at least 4 points, indicative of a minimally clinically important difference. Of the 15 patients for whom both EASI and DLQI change scores were available at the 8 to 12 week follow-up, 6 (54.6%) reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

Table 21 DLQI scores at the 8 to 12 week follow-up

		Stratification							
		All (*n*=17)	Age group			Immunosuppressant use at enrolment		Gender	
			Younger Adults (*n*=8)	Middle-aged Adults (*n*=2)	Older Adults (*n*=7)	No (*n*=6)	Yes (*n*=11)	Female (*n*=2)	Male (*n*=15)
DLQI rating at the 8 to 12 week follow-up									
Mean (SD)	**DLQI score**	4.88 (6.00)	6.00 (8.54)	5.50 (0.71)	3.43 (2.57)	6.50 (9.95)	4.00 (2.37)	4.00 (5.66)	5.00 (6.22)
Frequency (n, % within stratification group)	**No impact**	4 (23.5%)	3 (37.5%)	0	1 (14.3%)	2 (33.3%)	2 (18.2%)	1 (50.0%)	3 (20.0%)
	Small impact	8 (47.1%)	3 (37.5%)	1 (50.0%)	4 (57.1%)	2 (33.3%)	6 (54.5%)	0	8 (53.3%)
	Moderate impact	4 (23.5%)	1 (12.5%)	1 (50.0%)	2 (28.6%)	1 (16.7%)	3 (27.3%)	1 (50.0%)	3 (20.0%)
	Very large impact	0	0	0	0	0	0	0	0
	Extremely large impact	1 (5.9%)	1 (12.5%)	0	0	1 (16.7%)	0	0	1 (6.7%)
Change in DLQI severity between baseline and the 8 to 12 week follow-up									
		All (*n*=17)	**Younger Adults** (*n*=8)	**Middle-aged Adults** (*n*=2)	**Older Adults** (*n*=7)	**No** (*n*=6)	**Yes** (*n*=11)	**Female** (*n*=2)	**Male** (*n*=15)
Mean (SD)	**Absolute change in DLQI score**	12.12 (6.32)	10.50 (6.37)	10.00 (0.00)	14.57 (6.88)	12.83 (10.90)	11.73 (2.28)	18.50 (2.12)	11.27 (6.23)
	Percentage change in DLQI score	74.56% (22.41%)	72.49% (30.77%)	64.58% (2.95%)	79.77% (12.75%)	73.45% (35.76%)	75.16% (12.77%)	85.71% (20.20%)	73/07% (22.91%)
Frequency (n, % within stratification group)	**MCID reduction**	15 (88.2%)	6 (75.0%)	2 (100%)	7 (100%)	4 (66.7%)	11 (100%)	2 (100%)	13 (86.7%)
		All (*n*=11)	**Younger Adults** (*n*=6)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=4)	**No** (*n*=5)	**Yes** (*n*=6)	**Female** (*n*=2)	**Male** (*n*=9)
	DLQI MCID and EASI 50% reduction or greater	6 (54.6%)	3 (50.0%)	1 (100%)	2 (50.0%)	2 (40.0%)	4 (100%)	2 (100%)	4 (44.4%)

20+ week follow-up DLQI scores were available for a total of 11 patients and the full and stratified results are reported in Table 22. The mean DLQI score was 4.09 (SD = 3.70; range = 0 to 10), indicating a 'small impact' of AD on patients' lives. Almost three quarters of patients for whom data were available at this time point reported scored corresponding to small (45.5%) or no (27.3%) impact.

Of the patients with a 20+ week follow-up DLQI score, 2 did not have baseline DLQI scores reported, thus the comparison sample totaled 9 patients. The mean change in DLQI score was an improvement of 12.44 points (SD= 3.40; range = a reduced impact of 7 points to 29 points), or 79.22% (SD= 19.78%; range = a reduced impact of 41.18% to 100%) between baseline and the follow-up 20 or more weeks from the first injection. All 9 patients reported a reduction in impact of at least 4 points, indicative of a minimally clinically important difference. Of the 6 patients for whom both EASI and DLQI change scores were available at the 20+ weeks follow-up, 5 (83.33%) reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

Table 22 DLQI scores at the 20 or more week follow-up

		Stratification							
		All (*n*=11)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=5)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=4)	**No** (*n*=3)	**Yes** (*n*=8)	**Female** (*n*=3)	**Male** (*n*=7)
DLQI rating at the 20 weeks or more follow-up									
Mean (SD)	**DLQI score**	4.09 (3.70)	5.00 (4.53)	3.00 (*n/a*)	2.00 (1.63)	2.00 (2.00)	4.88 (3.98)	7.33 (3.79)	2.00 (1.91)
Frequency (n, % within stratification group)	**No impact**	3 (27.3%)	2 (40.0%)	0	1 (25.0%)	1 (33.3%)	2 (25.0%)	0	3 (42.9%)
	Small impact	5 (45.5%)	1 (20.0%)	1 (100%)	3 (75.0%)	2 (66.7%)	3 (37.5%)	1 (33.3%)	4 (57.1%)
	Moderate impact	3 (27.3%)	2 (40.0%)	0	0	0	3 (37.5%)	2 (66.7%)	0
	Very large impact	0	0	0	0	0	0	0	0
	Extremely large impact	0	0	0	0	0	0	0	0
Change in DLQI severity between baseline and the 20 weeks or more follow-up									
		All (*n*=9)	**Younger Adults** (*n*=5)	**Middle-aged Adults** (*n*=1)	**Older Adults** (*n*=3)	**No** (*n*=2)	**Yes** (*n*=7)	**Female** (*n*=3)	**Male** (*n*=6)
Mean (SD)	**Absolute change in DLQI score**	12.44 (3.40)	11.20 (3.35)	17.00 (*n/a*)	13.00 (3.00)	13.00 (4.24)	12.29 (3.50)	12.67 (5.13)	12.33 (2.80)
	Percentage change in DLQI score	79.22% (19.78%)	71.60% (24.00%)	85.00% (*n/a*)	90.00% (8.82%)	91.67% (11.79%)	75.67% (20.79%)	62.35% (21.95%)	87.66% (13.32%)
Frequency (n, % within stratification group)	**MCID reduction**	9 (100%)	5 (100%)	1 (100%)	3 (100%)	2 (100%)	7 (100%)	3 (100%)	6 (100%)

		All (*n*=6)	Younger Adults (*n*=4)	Middle-aged Adults (*n*=1)	Older Adults (*n*=1)	No (*n*=1)	Yes (*n*=5)	Female (*n*=3)	Male (*n*=3)
	DLQI MCID and EASI 50% reduction or greater	5 (83.33%)	3 (75.0%)	1 (100%)	1 (100%)	1 (100%)	4 (80.0%)	2 (66.7%)	3 (100%)

Note: Age was not reported for two patients, and gender for one patient, for whom 20+ weeks DLQI scores were available.

5.4.4. *Clinician-rated treatment response at all other follow-ups*

The most common clinician-rated treatment response for the 23 patients for whom data were available at the 2 to 4 week follow-up was 'somewhat better' (47.8%), followed closely by 'much better' (43.5%). One middle-aged female patient using immunosuppressants at the time of enrolment, was rated as having worse signs and symptoms, while a further middle-aged male patient using immunosuppressants at the time of enrolment was rated as showing no change. Full and stratified results are reported in Table 23.

Table 23 Clinician-rated treatment response scores at the 2 to 4 week follow-up

		Stratification							
		All (*n*=23)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=4)	**Middle-aged Adults** (*n*=7)	**Older Adults** (*n*=12)	**No** (*n*=11)	**Yes** (*n*=12)	**Female** (*n*=6)	**Male** (*n*=17)
Clinician rated response to treatment at the 2 to 4 week follow-up									
Frequency (n, % within stratification group)	**Much worse**	0	0	0	0	0	0	0	0
	Worse	1 (4.3%)	0	1 (14.3%)	0	0	1 (8.3%)	1 (16.7%)	0
	About the same	1 (4.3%)	0	1 (14.3%)	0	0	1 (8.3%)	0	1 (5.9%)
	Somewhat better	11 (47.8%)	2 (50.0%)	4 (57.1%)	5 (41.7%)	4 (36.4%)	7 (58.3%)	2 (33.3%)	9 (52.9%)
	Much better	10 (43.5%)	2 (50.0%)	1 (14.3%)	7 (58.3%)	7 (63.6%)	3 (25.0%)	3 (50.0%)	7 (41.2%)

The most common clinician-rated treatment response for the 19 patients for whom data were available at the 4 to 8 week follow-up was 'much better' (57.9%). One female older adult who was not using immunosuppressants at the time of enrolment was rated as having worse signs and symptoms, while a further two younger males were rated as showing no change. Full and stratified results are reported in Table 24.

Table 24 Clinician-rated treatment response scores at the 4 to 8 week follow-up

Stratification			
All (*n*=19)	**Age group**	**Immunosuppressant use at enrolment**	**Gender**

			Younger Adults (*n*=6)	Middle-aged Adults (*n*=4)	Older Adults (*n*=8)	No (*n*=9)	Yes (*n*=10)	Female (*n*=6)	Male (*n*=13)
Clinician rated response to treatment at the 4 to 8 week follow-up									
Frequency (n, % within stratification group)	**Much worse**	0	0	0	0	0	0	0	0
	Worse	1 (5.3%)	0	0	1 (12.5%)	1 (11.1%)	0	1 (16.7%)	0
	About the same	2 (10.5%)	2 (33.3%)	0	0	1 (11.1%)	1 (10.1%)	0	2 (15.4%)
	Somewhat better	5 (26.3%)	0	2 (50.0%)	2 (25.0%)	2 (22.2%)	3 (30.0%)	2 (33.3%)	3 (23.1%)
	Much better	11 (57.9%)	4 (66.7%)	2 (50.0%)	5 (62.5%)	5 (55.6%)	6 (60.0%)	3 (50.0%)	8 (61.5%)

Note: Age was not reported for one patient for whom 4 to 8 week clinician-rated treatment response scores were available.

All clinician-rated treatment response for the 20 patients for whom data were available at the 8 to 12 week follow-up indicated improvement in signs and symptoms, with 80% patients rated as being 'much better'. Full and stratified results are reported in Table 25.

Table 25 Clinician-rated treatment response scores at the 8 to 12 week follow-up

		Stratification							
		All (*n*=20)	**Age group**			**Immunosuppressant use at enrolment**		**Gender**	
			Younger Adults (*n*=7)	**Middle-aged Adults** (*n*=3)	**Older Adults** (*n*=10)	**No** (*n*=8)	**Yes** (*n*=12)	**Female** (*n*=3)	**Male** (*n*=17)
Clinician rated response to treatment at the 8 to 12 week follow-up									
0Frequency (n, % within stratification group)	**Much worse**	0	0	0	0	0	0	0	0
	Worse	0	0	0	0	0	0	0	0
	About the same	0	0	0	0	0	0	0	0
	Somewhat better	4 (20.0%)	0	1 (33.3%)	3 (30.0%)	0	4 (33.3%)	1 (33.3%)	3 (17.6%)
	Much better	16 (80.0%)	7 (100%)	2 (66.7%)	7 (70.0%)	8 (100%)	8 (66.7%)	2 (66.7%)	14 (82.4%)

Very few (*n*=5) clinician-rated treatment responses were available 20 weeks or more after the first injection. The majority were rated as being 'much better' (80%), with one older female who had not been using immunosuppressants at enrolment rated as showing no change. Full and stratified results are reported in Table 26.

Table 26 Clinician-rated treatment response scores at the 20 or more week follow-up

Stratification			
All (*n*=5)	**Age group**	**Immunosuppressant use at enrolment**	**Gender**

			Younger Adults (*n*=1)	Middle-aged Adults (*n*=0)	Older Adults (*n*=4)	No (*n*=2)	Yes (*n*=3)	Female (*n*=1)	Male (*n*=4)
Clinician rated response to treatment at the 20 weeks or more follow-up									
Frequency (n, % within stratification group)	**Much worse**	0	0	0	0	0	0	0	0
	Worse	0	0	0	0	0	0	0	0
	About the same	1 (20.0%)	0	0	1 (25.0%)	1 (50.0%)	0	1 (100%)	0
	Somewhat better	0	0	0	0	0	0	0	0
	Much better	4 (80.0%)	1 (100%)	0	3 (75.0%)	1 (50.0%)	3 (100%)	0	4 (100%)

5.4.5. *Relationships between endpoints at all other follow-ups*

Pearson's correlations were used to assess the strength and direction of any relationships between the endpoints.

At the 2 to 4 week follow-ups, correlations were limited by small sample sizes (see Table 27). However, significant strong positive relationships were observed between EASI and IGA adopting a Bonferroni-corrected alpha of $p<0.008$ to account for the multiple comparisons. No other relationship met this criterion, however this is likely because the analyses were underpowered, and with the exception of the relationship between EASI and DLQI scores, are in the direction expected.

Table 27 Correlations between severity scores at the 2 to 4 week follow-up

Measure	EASI at the 2 to 4 week follow-up	IGA at the 2 to 4 week follow-up	DLQI at the 2 to 4 week follow-up	Clinician-rated response at the 2 to 4 week follow-up
EASI at the 2 to 4 week follow-up				
IGA at the 2 to 4 week follow-up	0.81 (*p*=0.005; *n*=10)			
DLQI at the 2 to 4 week follow-up	0.06 (*p*=0.817; *n*=16)	0.42 (*p*=0.056; *n*=21)		
Clinician-rated response at the 2 to 4 week follow-up	-0.27 (*p*=0.726; *n*=4)	-0.74 (*p*=0.010; *n*=11)	-0.17 (*p*=0.546; *n*=15)	

At the 4 to 8 week follow-ups, correlations were, again, limited by small sample sizes (see Table 28). Adopting a Bonferroni-corrected alpha of p<0.008 to account for the multiple comparisons, only the strong positive relationship between IGA and DLQI severity scales were considered statistically significant. Again, the analyses were likely underpowered, and other relationships observed were in the direction expected.

Table 28 Correlations between severity scores at the 4 to 8 week follow-up

Measure	EASI at the 4 to	IGA at the 4 to 8	DLQI at the 4 to	Clinician-rated

	8 week follow-up	week follow-up	8 week follow-up	response at the 4 to 8 week follow-up
EASI at the 4 to 8 week follow-up				
IGA at the 4 to 8 week follow-up	0.59 (*p*=0.043; *n*=12)			
DLQI at the 4 to 8 week follow-up	0.50 (*p*=0.034; *n*=18)	0.76 (*p*=0.001; *n*=16)		
Clinician-rated response at the 4 to 8 week follow-up	-0.55 (*p*=0.065; *n*=12)	-0.66 (*p*=0.028; *n*=11)	-0.63 (*p*=0.009; *n*=16)	

At the 8 to 12 week follow-up, correlations were, again, limited by small sample sizes (see Table 29). As with the 2 to 4 week follow-up, adopting a Bonferroni-corrected alpha of p<0.008 to account for the multiple comparisons, only the strong positive relationship between EASI and IGA severity scales was considered statistically significant. Again, the analyses were likely underpowered, and other relationships observed were in the direction expected with the exception of that between EASI and DLQI, and the DLQI and clinician-rated treatment responses.

Table 29 Correlations between severity scores at the 8 to 12 week follow-up

Measure	EASI at the 8 to 12 week follow-up	IGA at the 8 to 12 week follow-up	DLQI at the 8 to 12 week follow-up	Clinician-rated response at the 8 to 12 follow-up
EASI at the 8 to 12 week follow-up				
IGA at the 8 to 12 week follow-up	0.85 (*p*=0.008; *n*=8)			
DLQI at the 8 to 12 week follow-up	-0.06 (*p*=0.864; *n*=11)	0.64 (*p*=0.018; *n*=13)		
Clinician-rated response at the 8 to 12 week follow-up	-0.27 (*p*=0.452; *n*=10)	-0.70 (*p*=0.012; *n*=12)	0.05 (*p*=0.861; *n*=15)	

No correlations were performed for the 20 weeks or more follow-up as for no comparison was there data available for more than 10 patients.

5.4.6. *Management and reporting of Adverse events/adverse reactions*

This retrospective clinical notes review study is based on the secondary use of data for which individual safety data capture and expedited reporting of Pharmacovigilance data is not required. The proactive capture and follow up of Pharmacovigilance data was performed throughout the duration of the EAMS from first patient enrolment until Marketing Authorisation (MA).

This retrospective study did not collect Pharmacovigilance data, as such data was previously provided to the Pharmacovigilance unit. However the raw study data was shared with the Pharmacovigilance [PV] department to review for any omitted PV data and or the presence of any safety signal.

The PV review of raw data highlighted that a single PV report was overlooked and not reported during the EAMS programme. This case [PV case number: *2018SA207745*] of localized acute eczema was subsequently reported and recorded in the PV database.

There were no PV signals detected during this study.

6. DISCUSSION

6.1. Key results

In line with the objectives stated, the key results were as follows.

On average, AD severity, as measured by both EASI and IGA scales, decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. EASI scores improved by a mean of 14.13 points, or 56%, with two thirds of patients (66.7%) demonstrating a reduction of 50% or more (meeting the EASI-50 criteria), and 73% demonstrating a minimally clinically important difference of 6.6 points or more. IGA scores improved by at least two categories for 75% patients, and by one category for 17.9%, with no change for one patient and an increase in severity for one patient.

On average, the impact of AD on patients' lives, as measured by the DLQI, also decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up. DLQI scores improved by a mean of 8.98 points, or 59%, with 80% patients demonstrating a minimally clinically important improvement of at least 4 points. 53% patients reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores.

For 85% patients, clinicians rated the treatment response as being either 'better' (19%) or 'much better' (65%).

Analysis of other timeframes demonstrated similar results but interpretation is limited due to small sample sizes.

6.2. Interpretation

This is the first UK real world analysis of treatment outcomes for patients treated with dupilumab in clinical practice. We observed a statistically significant improvement in AD disease severity as measured by EASI and IGA between baseline and a 16 $^{+/-4}$ week follow-up period, with two thirds of patients (66.7%) demonstrating a reduction of 50% or more (meeting the EASI-50 criteria).

On average, the impact of AD on patients' lives, as measured by the DLQI, also decreased by a statistically significant level between baseline and the 16 $^{+/-4}$ week follow-up.

53% patients reported both a reduction in EASI scores of 50% or more, and a minimally clinically important reduction in DLQI scores. The data from EAMS shows that patients achieved improvements in EASI, IGA and DLQI scores just 2-4 weeks after the first injection. Our economic model used 16 weeks as the timepoint for assessment of response; these data suggest that responses are seen earlier.

Most clinicians rated the treatment response as being either 'better' or 'much better' after treatment with dupilumab. This data supports the use of dupilumab in a clinical practice setting.

Table 5. Patients meeting EASI-50 response criteria in RCTS compared to real-world EAMS study Clinical setting

Clinical Setting	Q2W dosing (n)	EASI-50
CHRONOS trial (at 16 weeks)	106	80%
CAFÉ trial	107	85%

(at 16 weeks)		
EAMS (at 16 weeks +/- 4 weeks)	35	66.7%

Note that this data was collected retrospectively outside of a controlled setting, and there were differences in patient baseline characteristics, therefore data must not be directly compared with results from other studies including the pivotal trials.

These emerging data from EAMS provide further support of dupilumab sustained benefit. Furthermore, past immunosuppressant use was reported for 91.2% of EAMS patients (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different types of immunosuppressant. The EAMS patients are real world patients who were more likely to have complicating issues and difficult-to-treat disease.

6.3. Generalizability

The entry criteria into the dupilumab EAMS was stricter than the licensed indication of dupilumab therefore results are not generalisable to the population of patients who may be prescribed dupilumab in the real world. Patients enrolled into EAMS were generally more severe, with the majority of patients having failed on more than one systemic immunosuppressant prior to commencing treatment with dupilumab. Furthermore, given differences in baseline characteristics, clinical setting and lack of a control group, the results should not be directly compared with clinical studies.

The HRA re-classification of this study as ‘research’ was based on the potential generalisability of data.

6.4. Limitations

As with any retrospective study based on secondary use of data, the interpretation of the results of this study and interpretation of study endpoints has depended on the completeness and quality of the source medical records and the reliability of the abstraction of data from the medical records.

This study is retrospective in nature and as such is limited by the lack of control group, lack of randomization and the completeness of data available. Due to the volume of missing data, no imputations were performed. Due to small sample sizes the majority of analyses were descriptive only. It is possible that patients without follow-up data were more likely to be those who had not responded as well to treatment.

7. CONCLUSIONS

The key conclusion of the study is that use of dupilumab improves signs and symptoms of atopic dermatitis, and the impact that AD has on quality of life. This is of particular significance given that the EAMS patients had severe disease at baseline that was hard to treat, as indicated by their treatment history and inclusion in EAMS as judged by their clinician.

8. OTHER INFORMATION

8.1. Ethical considerations

8.1.1. *Ethical principles*

This study received a favorable opinion from the HRA: 19/HRA/0017. Note that the study was re-classified by the HRA from ‘non-research’ to ‘research’ in April 2018, therefore, the application was made to the HRA after study start. Approval was received prior to analysis and reporting of data.

This is a retrospective analysis of baseline data. It was not necessary to seek patient consent (already obtained at the start of EAMS), and the study did not require EC approval. Anonymised data was obtained direct from the patients care team.

8.1.2. *Laws and regulations*

This study was conducted in accordance in accordance with local regulations, including local data protection regulations and, where appropriate, in accordance with standard operating procedures set out by Sanofi.
This study was approved by the NHS Health Research Authority (Reference: 19/HRA/0017, 10th April 2018). All necessary local Trust approvals were obtained.

8.1.3. *Data protection*

All study participants provided informed consent. Pseudonymised data entered into CRFs were downloaded from emails and stored and analysed on a password-, virus- and firewall- protected LAN network drive with a central hard drive at the University of York. All emails containing data were subsequently deleted. Data will not be shared with other organisations. No use of the data collected for the study will be possible without the authorisation of Sanofi (see contract).

8.1.4. *Record retention*

Electronic records from this project will be retained securely for 5 years from study completion.

8.1.5. *The Company audits and inspections by Competent Authorities (CA)*

The following were covered in contractual agreements with the Trusts prior to initiation of the study:
The Trust shall permit the Sponsor (or its authorised representatives) access to conduct an audit of the Trust's operations, facilities, procedures and/or systems (but only to the extent that these relate to the performance of its obligations under the Agreement) to ensure that the Trust is in compliance with its obligations under the Agreement, such access to be arranged at mutually convenient times and on reasonable notice. Such audit may take such form as the Sponsor reasonably thinks appropriate including the right to inspect any facility being used for the conduct of the Study and to examine any procedures or records relating to the Study, in accordance with the provisions of clause 6.2 of the Agreement.
The Trust shall promptly inform the Sponsor of any intended or actual inspection, written enquiry and/or visit to the Trust's premises by any regulatory authority in connection with the Study and forward to the Sponsor copies of any correspondence from any such regulatory authority relating to the Study. The Trust will use all reasonable endeavours to procure that the Sponsor may have a representative present during any such visit.

8.2. Ownership of data and use of registry results

The ownership of data was agreed contractually between Sanofi and the Trusts. Saofi have obtained permission to use anonymised, collated data provided to support the dupilumab Health Technology Appraisal ("HTA"). The report will be made available to employees of the Trust on request and may be used for local/regional presentation. It may not be published without the prior written approval of Sanofi.

8.3. Study consultants

8.3.1. *Investigators*

Dr. Michael Ardern-Jones – University Hospital Southampton NHS Foundation Trust
Dr. Donal O'Kane – Belfast Health and Social Care Trust
Dr. Shireen Velangi – University Hospitals Birmingham NHS Foundation Trust
Dr. Lindsay Shaw – University Hospitals Bristol NHS Foundation Trust
Dr. Carolyn Charman – Royal Devon and Exeter NHS Foundation Trust
Dr. Philip Laws – Leeds Teaching Hospitals NHS Trust
Dr. Hywel Cooper – Portsmouth Hospitals NHS Trust
Dr. Michael Cork – Sheffield Teaching Hospitals NHS Foundation Trust

8.3.2. *Other responsible parties*

Adam Smith – York Health Economics Consortium

8.3.3. *Scientific Committee and Charter*

Scientific Advisor, Dermatology – Lauren Davis
Associate Medical Director, Dermatology – Raj Rout
Sponsor Principal Health Outcomes Manager – Richard Hudson

8.3.4. *Contract Research Organisation (CRO)*

Sanofi commissioned York Health Economics Consortium (YHEC, Enterprise House, Innovation Way, University of York, Heslington, York, YO10 5NQ) to coordinate the conduct of this study, including management of retrospective data collection and monitoring, statistical analyses, presentation of the results and production of the Study Report.

9. REFERENCES

1. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. British Journal of Dermatology. 2015 May 1;172(5):1353-7.
2. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean?. Journal of Investigative Dermatology. 2005 Oct 31;125(4):659-64.
3. Schram ME, Spuls PhI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minmal clinically important difference. European Journal of allergy and Clinical Immunology. 2012; 67: 99-106.
4. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. Dermatology. 2015; 230(1): 27-33
5. Mukaka MM. A guide to appropriate use of correlation coefficient in medical research. Malawi Medical Journal. 2012;24(3):69-71.

10. APPENDICES

10.1. Appendix A

Table A1 below provides additional descriptive statistics for all continuous variables.

Variable	N	Mean	Std. Error of Mean	Median	Mode	Std. Deviation	Minimum	Maximum	Interquartile range	
									25th	75th
EASI										
EASI: baseline	55	27.93	1.77	27.10	32.00	13.09	4.30	72.00	19.80	35.60
EASI: 2 to 4 week follow-up	16	7.98	3.36	3.30	0.00	13.45	0.00	54.00	0.30	8.45
EASI: 4 to 8 week follow-up	19	9.57	2.39	6.60	.00[a]	10.42	0.00	35.00	2.30	12.80
EASI: 8 to 12 week follow-up	12	10.78	3.39	8.05	0.00	11.74	0.00	40.20	2.23	18.83
EASI: 16$^{+/-4}$ week follow-up	32	7.62	1.11	7.50	0.00	6.26	0.00	21.60	2.43	11.70
EASI: 20 or more week follow-up	8	4.40	1.33	4.10	4.10	3.76	0.50	12.00	1.23	6.50

Absolute reduction from baseline in EASI: 2 to 4 week follow-up	16	18.87	3.94	13.40	3.20[a]	15.74	3.20	53.90	5.08	34.70
Absolute reduction from baseline in EASI: 4 to 8 week follow-up	17	16.46	3.11	18.40	-4.60[a]	12.82	-4.60	40.50	4.65	23.25
Absolute reduction from baseline in EASI: 8 to 12 week follow-up	12	23.71	3.85	20.65	4.30[a]	13.32	4.30	57.90	18.10	28.45
Absolute reduction from baseline in EASI: $16^{+/-4}$ week follow-up	30	14.13	1.96	15.05	9.20	10.71	-9.10	33.10	5.03	23.98
Absolute reduction from baseline EASI: 20 or more week follow-up	7	16.44	4.49	16.80	2.00[a]	11.89	2.00	31.50	3.00	29.50
Percentage reduction from baseline in EASI: 2 to 4 week follow-up	16	68.33	7.78	78.56	100.00	31.12	17.92	100.00	36.29	99.11
Percentage reduction from baseline in EASI: 4 to 8 week follow-up	17	60.25	8.96	72.35	100.00	36.94	-16.79	100.00	45.79	84.71
Percentage reduction from baseline in EASI: 8 to 12 week follow-up	12	71.63	7.30	71.20	100.00	25.30	16.93	100.00	53.56	94.57
Percentage reduction from baseline in EASI: $16^{+/-4}$ week follow-up	30	55.84	7.85	62.57	100.00	43.01	-79.82	100.00	42.84	86.57
Percentage reduction from baseline in EASI: 20 or more week follow-up	7	72.99	9.76	79.25	21.74[a]	25.82	21.74	97.75	61.22	91.38
DLQI										
DLQI: baseline	54	18.26	0.84	17.00	15.00	6.18	3.00	30.00	14.00	23.00
DLQI_2_4weeks	27	6.07	1.19	5.00	1.00	6.21	0.00	25.00	1.00	10.00
DLQI: 4 to 8 week follow-up	23	6.30	1.39	5.00	0.00	6.68	0.00	30.00	1.00	9.00

DLQI: 8 to 12 week follow-up	17	4.88	1.45	4.00	2.00	6.00	0.00	26.00	1.50	6.00
DLQI: $16^{+/-4}$ week follow-up	42	7.86	1.46	4.00	0.00	9.49	0.00	39.00	1.00	12.50
DLQI: 20 or more week follow-up	11	4.09	1.12	3.00	.00[a]	3.70	0.00	10.00	1.00	9.00
Absolute reduction from baseline in DLQI: 2 to 4 week follow-up	26	13.15	1.56	12.00	12.00	7.96	0.00	29.00	6.75	18.75
Absolute reduction from baseline in DLQI: 4 to 8 week follow-up	21	10.95	1.71	11.00	8.00[a]	7.81	-3.00	29.00	6.50	15.00
Absolute reduction from baseline in DLQI: 8 to 12 week follow-up	17	12.12	1.53	11.00	10.00	6.32	1.00	29.00	9.50	15.00
Absolute reduction from baseline in DLQI: $16^{+/-4}$ week follow-up	40	8.98	1.25	10.00	6.00[a]	7.91	-14.00	29.00	6.00	13.75
Absolute reduction from baseline in DLQI: 20 or more week follow-up	9	12.44	1.13	13.00	7.00[a]	3.40	7.00	17.00	9.50	15.50
Percentage reduction from baseline in DLQI: 2 to 4 week follow-up	26	68.79	5.89	78.68	100.00	30.05	0.00	100.00	45.33	93.33
Percentage reduction from baseline in DLQI: 4 to 8 week follow-up	21	61.76	7.51	61.90	100.00	34.44	-11.11	100.00	43.65	94.76
Percentage reduction from baseline in DLQI: 8 to 12 week follow-up	17	74.56	5.44	73.33	62.50[a]	22.41	3.70	100.00	65.15	90.28
Percentage reduction from baseline in DLQI: $16^{+/-4}$ week follow-up	40	58.85	6.66	73.38	100.00	42.11	-56.00	100.00	32.20	91.25
Percentage reduction from baseline in DLQI: 20 or more week follow-up	9	79.22	6.59	85.00	100.00	19.78	41.18	100.00	62.58	95.83

a. Multiple modes exist. The smallest value is shown

10.2. Appendix B

The results of the interim analysis conducted in April 2018 are presented in Appendix B. The interim analysis reported only on objectives which were required for the response to the NICE appraisal consultation document in April 2018. Following the interim analysis, a further case report was received and results were re-analysed to include the full data set, and to fulfil all objectives of the retrospective study.

1.1 Background

Sanofi has developed dupilumab, the first human monoclonal antibody indicated in the treatment of atopic dermatitis (AD). Dupilumab inhibits the signalling of interleukin-4 and interleukin-13 receptors, which are implicated in atopic or allergic diseases, such as AD. Dupilumab (Dupixent®) is indicated for treatment of moderate to severe AD in adult patients who are candidates for systemic therapy. Dupilumab can be used with or without topical therapies. Dupilumab has been shown in two randomised, placebo-controlled phase 3 trials involving patients with AD (SOLO 1 and SOLO 2)[7] to be superior to placebo in reducing the signs and symptoms of AD, such as the investigator's global assessment (IGA), pruritus, anxiety and depression, and improving patient quality of life.

The early access to medicines scheme (EAMS) provides an opportunity for patients with seriously debilitating conditions to access therapies that do not yet have marketing authorisation. When products are subsequently evaluated in health technology appraisals by the National Institute for Health and Care Excellence (NICE), data collected during the EAMS period can provide useful evidence for inclusion in the submission dossier, and to inform the reimbursement decision problem.

YHEC generated a brief report outlining the baseline characteristics of the patients enrolled to the EAMS scheme. Sanofi have requested an analysis of the available follow-up data for this cohort. These data will increase the understanding of the efficacy of dupilumab in a real-world population sample.

1.2 Objectives

This interim report outlines the preliminary follow-up data analysis of the EAMS cohort to provide evidence that may be used in the NICE submission of dupilumab. A full report will follow when the full dataset has been received. Placeholders have been used to indicate the analyses that are to follow.

[7] Simpson *et al.* Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016. DOI: 10.1056/NEJMoa1610020.

2.1 Data Processing

All EAMS data available on 18 April 2018 were entered by a single researcher into separate Excel templates for baseline and follow-up data. Where appropriate, for continuous variables, conditional formatting was used to highlight unexpected entries (i.e. entries outside the possible range of values), and for categorical inputs, drop-down boxes were used to ensure consistency of input. The following variables were captured at baseline:

- Patient ID;
- Patient demographics:
  - Age (years);
  - Sex;
  - Height (cm);
  - Weight (kg).
- Atopic dermatitis (AD) scores:
  - EASI score (eczema, area and severity index; possible scores range from 0 to 72, where higher scores indicate greater severity AD);
  - IGA score (investigator's global assessment score; possible scores range from 0 to 4, where higher scores indicate greater severity AD);
  - DLQI score (dermatology life quality index; possible scores range from 0 to 30, where higher scores indicate greater impact of AD on quality of life).
- Past and current AD treatments by class and active ingredient:
  - Immunosuppressants (e.g. azathioprine, methotrexate);
  - Topical corticosteroids (e.g. hydrocortisone);
  - Non-topical corticosteroids (e.g. prednisone);
  - Topical calcineurin inhibitors (e.g. tacrolimus);
  - Antihistamines (e.g. fexofenadine);
  - Antibiotics (e.g. phenoxymehylpenicillin);
  - Phototherapy (e.g. narrowband UVB);
  - Immunostimulants (e.g. interferon gamma);
  - Immunomodulators (e.g. apremilast);
  - Monoclonal antibodies (e.g. ustekinumab)
  - Retinoids (e.g. alitretinoin);
  - Intravenous immunoglobin.

For age variables that were missing or clearly erroneous (i.e. age implausible given other variables; *n*=2), a proxy age was calculated using the birth date and consent date.

For weight and height, decimals were rounded to the nearest whole number and in any cases where the measurements were reported in alternative units, units were converted to kg and cm.
For both baseline forms, where handwritten notes were illegible (*n*=19), forms were returned to the client securely for clarification.

A second researcher reviewed the data for unexpected entries and performed detailed checking of 10% entries.

The following data were captured at follow-up:

- Patient ID;
- Atopic dermatitis (AD) scores (at intervals by patient follow-up date):
    - EASI score (eczema area and severity index; possible scores range from 0 to 72, where higher scores indicate greater severity AD);
    - IGA score (investigator's global assessment score; possible scores range from 0 to 4, where higher scores indicate greater severity AD);
    - DLQI score (dermatology life quality index; possible scores range from 0 to 30, where higher scores indicate greater impact of AD on quality of life);
    - POEM score (patient-oriented eczema measure; possible scores range from 0-28, where higher scores indicate greater symptom burden).
- Response to treatment:
    - A narrative was provided on patient response to treatment as recorded in the patient notes. These notes were mapped to a 5 point Likert scale by the clinician.

Where required, IGA ratings were recoded. Ratings of '5' were assumed to be indicative of use of a different rating scale, where a score of 5 reflects most severe disease, and as such, these ratings were recategorised as '4'. Ratings across categories (e.g. a rating of 3 to 4) were assumed to reflect a severity that the clinician did not persistently consider in the higher category, and thus recategorised at the lower score.

Review dates were not provided for the 3-month follow-up for one site, thus proxy dates 3 months from baseline dates were estimated. EASI and DLQI scores for one patient were rated as '>35' and '>25' respectively. Under the assumption that the clinician regarded AD severity as greater than these values, but not persistently at a specific higher score, these were conservatively recoded as 36 and 26.

Data monitoring, whereby study site contacts with access to patient records verbally confirmed the accuracy of the data received at the analysis site, item by item, via the telephone, was to be completed for 20% data collection forms. Data monitoring is still ongoing.

2.2 Data Analysis

The data were then imported into SPSS for analysis. The analysis included descriptive statistics of the sample characteristics, dermatitis scores and past and current AD treatments. Specifically, for continuous variables (e.g. age, AD scores), average values (means with 95% confidence intervals, and medians) with appropriate measures of dispersion (standard deviation and interquartile range) were calculated.

Age was then categorised into the following groups:

- Young adults: 18 to 35 years;
- Middle-aged adults: 36 to 55 years;
- Older adults: 56 years and over.

Dermatitis scores were categorised as follows:

- IGA scores:
  - 0 = Clear;
  - 1 = Almost clear;
  - 2 = Mild disease;
  - 3 = Moderate disease;
  - 4 = Severe disease.
- EASI scores (as per Lesham et al., 2015[8]):
  - 0 = Clear;
  - 0.1 to 1.0 = Almost clear;
  - 1.1 to 7.0 = Mild disease;
  - 7.1 to 21.0 = Moderate disease;
  - 21.1 to 50.0 = Severe disease;
  - 51.0 to 72.0 = Very severe disease.
- DLQI scores (as per Hongbo et al., 2005 [9]):
  - 0 to 1 = No effect on patient's life;
  - 2 to 5 = Small effect on patient's life;
  - 6 to 10 = Moderate effect on patient's life;
  - 11 to 20 = Very large effect on patient's life;
  - 21 to 30 = Extremely large effect on patient's life.

For other variables (e.g. sex, past and current treatments), frequencies and proportions were calculated.

Analysis of demographics (age and sex) and categorised dermatitis severity scores (IGA, EASI) were reported for the sample as a whole, and split by past immunosuppressant use. This was first reported by total number of immunosuppressants previously used, and then by type of immunosuppressant previously used with respect to:

- Methotrexate;
- Azathioprine;
- Ciclosporin;
- Mycophenolate mofetil;
- Other immunosuppressants.

Height and weight variables were not analysed.

The following analyses were conducted to compare follow-up and baseline data:

- Percentage change in severity for EASI, IGA and DLQI scores.

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[8] Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. British Journal of Dermatology. 2015 May 1;172(5):1353-7.

[9] Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean?. Journal of Investigative Dermatology. 2005 Oct 31;125(4):659-64.

- Absolute change in severity score for EASI, IGA and DLQI scores.
- A comparison of change in scores for those patients taking immunosuppressants compared to patients not taking these medications.
- A correlational analysis of changes between endpoints.

These analyses were conducted for the full follow-up period and then specifically for patients with a complete record at 3 months. Patient response to treatment over time was reported graphically.

The clinicians' rating of patient of treatment response, and published minimal clinically important differences (MCID) for EASI and POEM[10], as well as the DLQI[11], were used to provide a qualitative interpretation of change in patient scores from baseline.

Analyses were sense-checked and transcription errors reviewed by a second researcher.

[10] Schram ME, Spuls PhI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minmal clinically important difference. European Journal of allergy and Clinical Immunology. 2012; 67: 99-106.

[11] Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. Dermatology. 2015; 230(1): 27-33.

3.1 Available Data

Due to reclassification of the follow-up project by the Health Research Authority, research activities were put on hold for all sites, until approval was received by the site research and development departments. As a result of these delays, follow-up data was available for 7 or the 8 sites.

At the time of this report, data monitoring has been competed for 3 sites, totalling 6 patients (11% of the available sample) and is ongoing for the remaining sites. To date, no inaccuracies have been identified, thus we are confident in the validity of the data.

3.2 Baseline Demographics

<< Full details of characteristics and treatment history of the total baseline sample will be included in the full report when the full sample are available. >>

3.2.1 Characteristics of follow-up sample

For the preliminary analysis follow-up data were available for a total of 56 patients, comprising 19 (33.9%) females, 36 males (65.5%) with a mean age of 42.9 years (range: 20 to 76 years) and one patient for whom age and gender was not reported. Past immunosuppressant use was reported for 93% (52 patients), and current use for 52% (29 patients) of the follow-up sample.

3.3 3 Month Follow-Up

3.3.1 Change in IGA Severity

IGA data were available for 35 patients at the 3 month follow-up time point. Of these, 5 patients did not have baseline IGA scores. At the three month follow-up, only one patient (2.9%) had a score of 4 (severe disease) and 4 (11.4%) had a score of 3 (moderate disease). The remaining patient had scores indicating clear skin or mild disease, with 10 patients (28.6%) with a score of 2 (mild disease), the majority (15 patients; 42.9%) with a score of 1 (almost clear), while 5 (14.3%) had a score of 0 indicating that the AD had cleared. Table 1 shows the 3 month IGA score stratified by age.

Table 1: IGA score at 3 months stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Clear	2	1	2	3	2
Almost clear	4	4	7	7	8
Mild disease	3	3	3	3	7
Moderate disease	0	2	2	1	3
Severe disease	0	0	1	1	0

Note: Age was not reported for one patient.

Of the 33 patients with baseline and 3 month IGA scores, only 1 (3.3%) had shown an increase in severity category (worsened by 1 category) and 1 (3.3%) had had no change in IGA category. 8 patients (26.7%) had improved by one category, with the remaining 20 patients (66.7%) improving by two categories or more. Table 2 shows these changes stratified by age and whether immunosuppressant use was reported at the time of enrolment.

Table 2: IGA score at 3 months stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Increase in severity	0	1	0	0	1
No change in severity	0	0	1	1	0
Improvement by one category	1	2	5	4	4
Improvement by two or more categories	6	7	7	9	11

Note: Age was not reported for one patient.

3.3.2 Change in EASI Severity

EASI data were available at the second follow-up time point for a total of 35 patients. This follow-up was on average 86 days (mean; median: 97 days; range: 17 days to 182 days) or approximately 3 months after the date of the first injection. For one site (6 patients), the second follow-up occurred closer to three weeks after the first injection (17 to 29 days). At second follow-up, the mean EASI score was 7.5 (SD: 7.5; range: 0.0 to 35.0), at the lower end of the 'moderate disease' category.

Of patients with EASI scores at second follow-up, 2 patients did not have baseline EASI scores, leaving 33 patients for follow-up comparisons. The mean change in EASI score was an improvement of 19.0 points (SD: 14.4; range: -9.1 to 53.9), or 62.5% (SD: 42.0%; range: -79.8% to 100%) reduction in severity. In total, 24 patients (72.7%) showed a reduction of 50% in EASI scores, and 26 (78.8%) had at least a 6.6 point reduction, indicative of a minimally clinically important difference at the 3 month time point.

A Wilcoxon Signed Ranks test was used to statistically compare the EASI score at second follow-up with that at baseline for all patients with both scores available. This revealed that EASI scores were significantly lower at the second follow-up, with a median value of 6.1 (range 0.0 to 35.0), than at baseline, where EASI scores were a median of 24.9 (range 4.3 to 72.0; Z=-4.8, p<0.001).

Table 1: EASI Scores at second follow-up stratified by age and immunosuppressant use at time of enrolment

	Stratification					
	Full cohort	Age group			Immunosuppressant use	
		Younger Adults	Middle-aged Adults	Older Adults	No	Yes
Mean (SD) EASI score at 3 months	7.5 (7.5)	7.8 (6.7)	6.1 (4.0)	7.9 (10.8)	7.0 (9.5)	7.9 (5.6)
Mean (SD) change in EASI score	19.0 (14.4)	17.9 (16.7)	15.6 (12.8)	22.9 (12.8)	22.6 (15.5)	15.6 (12.8)
Mean (SD) percentage change in EASI score	62.5% (42.0%)	64.7% (15.1%)	51.7% (46.4%)	25.1% (14.1%)	69.2% (45.8%)	56.4% (38.5%)
Frequency (n, % within subgroup) with MCID reduction	26 (78.8%)	8 (80.0%)	7 (63.6%)	10 (90.9%)	13 (81.3%)	13 (76.4%)
Frequency (n, % within subgroup) with 50% reduction in EASI scores	24 (72.7%)	5 (50.0%)	8 (72.7%)	10 (90.9%)	14 (87.5%)	10 (58.8%)

Note: Age was not reported for one patient.

3.3.3 Change in DLQI Severity

DLQI data were available for 46 patients at the 3 month follow-up time point. The mean DLQI score was 6.7 points (SD: 8.1; range: 0.0 to 39.0), indicating the disease, on average, had a moderate effect on the patients' lives.

Of those with available DLQI data at 3 months, 2 patients did not have baseline DLQI scores, resulting in 44 patients for the follow-up comparisons. The mean change in DLQI scores was an improvement of 11.0 points (SD: 8.2; range: -14.0 to 29.0), or a 65.4% (SD: 37.0%; range -56.0% to 100.0%) reduction in the impact on quality of life. 39 patients (88.6%) had at least a four point reduction, indicative of a minimal clinically important difference at the 3 month time point.

32 of the patients with DLQI data at baseline and 3 month follow-up also had EASI data at baseline and 3 month follow-up. Of these, 21 (65.6%) had achieved both a minimally clinically significant difference in the DLQI and a reduction in EASI severity of 50% of more. Table 4 shows these changes stratified by age and immunosuppressant use reported at the time of enrolment.

Table 4: DLQI Scores at 3 months stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Mean (SD) DLQI score	6.6 (6.7)	8.8 (11.3)	5.1 (6.4)	5.5 (5.6)	7.6 (9.2)
Mean (SD) change in DLQI score	10.3 (4.9)	9.6 (11.3)	12.9 (7.4)	13.3 (8.4)	9.0 (9.5)
Mean (SD) percentage change in DLQI score	67.3% (26.3%)	53.7% (49.6%)	73.8% (31.7%)	72.1% (31.1%)	59.4% (41.2%)
Frequency (n, % within subgroup) with MCID reduction	11 (91.66%)	11 (78.6%)	16 (94.1%)	19 (90.5%)	20 (87.0%)
Frequency (n, % within subgroup) with DLQI MCID reduction and EASI-50	4 (40.0%)	7 (77.8%)	9 (90.0%)	13 (81.3%)	8 (50.0%)

Note: Age was not reported for one patient. Only 32 patients had DLQI and EASI data.

3.4 All Follow-Up

The median time between baseline and the latest follow-up was 4.67 months (range: 3.96 to 9.8 months). The following results consider the change from baseline to the latest available follow up for each patient.

3.4.1 Change in IGA severity

IGA data were available for 39 patients using the latest follow-up time point. Of these, 5 patients did not have baseline IGA scores. At the latest follow-up, only one patient (2.6%) had a score of 4 (severe disease) and 5 (12.9%) had a score of 3 (moderate disease). The remaining patient had scores indicating clear skin or mild disease, with 10 patients (25.6%) with a score of 2 (mild disease), the majority (18 patients; 45.1%) with a score of 1 (almost clear), while 5 (12.8%) had a score of 0 indicating that the AD had cleared. Table 5 shows the latest IGA score stratified by age and recorded immunosuppressant use at enrolment.

Table 5: Latest IGA score stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Clear	1	1	3	4	1
Almost clear	4	6	7	8	10
Mild disease	4	3	3	2	8
Moderate disease	0	3	2	1	4
Severe disease	0	0	1	1	0

Note: Age was not reported for one patient.

Of the 34 patients with baseline and latest IGA scores, 2 (5.9%) had shown an increase in severity category (worsened by 1 category) and 1 (2.9%) had had no change in IGA category. 6 patients (17.6%) had improved by one category, with the remaining 25 patients (73.5%) improving by two categories or more. Table 6 shows these changes stratified by age and whether immunosuppressant use was reported at the time of enrolment.

Table 6: IGA categories at the latest time point stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Increase in severity	0	2	0	0	2
No change in severity	0	0	1	1	0
Improvement by one category	1	2	3	2	4
Improvement by two or more categories	6	9	10	12	13

Note: Age was not reported for one patient.

3.4.2 Change in EASI Severity

EASI data were available a total of 38 patients using the latest follow-up time point. Similarly to the results at the 3 month follow-up, the mean EASI score was 7.2 (SD: 8.2; range: 0.0 to 40.2), at the lower end of the 'moderate disease' category.

Of patients with follow-up EASI score, 2 patients did not have baseline EASI scores, leaving 36 patients for follow-up comparisons. Again, similar to the 3 month follow-up, the mean change in EASI score was an improvement of 19.0 points (SD: 13.8; range: -9.1 to 57.9), or 63.5% (SD: 41.3%; range: -79.8% to 100%) reduction in severity. In total, 26 patients (72.2%) showed a reduction of 50% in EASI scores, and 28 (77.8%) had at least a 6.6 point reduction, indicative of a minimally clinically important difference at the latest follow-up. Table 7 shows the EASI scores and changes scores at the latest follow-up stratified by age and reported immunosuppressant use at the time of enrolment.

Table 7: EASI scores at the latest follow-up stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	**Middle-aged Adults**	**Older Adults**	**No**	**Yes**
Mean (SD) EASI score	7.8 (6.7)	6.1 (4.0)	7.9 (10.8)	7.0 (9.5)	7.9 (5.6)
Mean (SD) change in EASI score	17.9 (16.7)	15.6 (12.8)	22.9 (12.8)	22.6 (15.5)	15.6 (12.8)
Mean (SD) percentage change in EASI score	64.7% (15.1%)	51.7% (46.4%)	25.1% (14.1%)	69.2% (45.8%)	56.4% (38.5%)
Frequency (n, % within subgroup) with MCID reduction	8 (80.0%)	7 (63.6%)	10 (90.9%)	13 (81.3%)	13 (76.4%)
Frequency (n, % within subgroup) with 50% reduction in EASI scores	6 (60.0%)	10 (76.9%)	9 (75.0%)	14 (82.4%)	12 (63.2%)

Note: Age was not reported for one patient.

3.4.3 Change in DLQI Severity

DLQI data were available for 50 patients at the latest follow-up time point. Similarly to at the 3 month follow-up, the mean DLQI score was 7.0 points (SD: 8.4; range: 0.0 to 39.0), indicating the disease, on average, had a moderate effect on the patients' lives.

Of those with available DLQI data at the latest follow-up, 2 patients did not have baseline DLQI scores, resulting in 48 patients for the follow-up comparisons. Similarly to the 3 month follow-up, the mean change in DLQI scores was an improvement of 10.6 points (SD: 8.3; range: -14.0 to 29.0), or a 65.8% (SD: 38.0%; range -56.0% to 100.0%) reduction in the impact on quality of life. 41 patients (73.2%) had at least a four point reduction, indicative of a minimal clinically important difference at the latest time point. Table 8 shows the latest DLQI scores and change scores stratified by age and whether patients were reported as using immunosuppressants at the time of enrolment.

As at the 3 month follow-up, 32 of the patients with DLQI data at baseline and latest follow-up also had EASI data at baseline and latest follow-up. Of these, 21 (65.6%) had achieved both a minimally clinically significant difference in the DLQI and a reduction in EASI severity of 50% of more.

Table 8: Latest DLQI scores stratified by age and immunosuppressant use at time of enrolment

	Age group			Immunosuppressant use	
	Younger Adults	Middle-aged Adults	Older Adults	No	Yes
Mean (SD) DLQI score	6.8 (5.7)	8.9 (10.7)	5.6 (8.3)	5.1 (6.5)	8.6 (9.5)
Mean (SD) change in DLQI score	10.0 (4.5)	9.5 (10.8)	12.2 (8.2)	13.8 (8.1)	8.0 (7.7)
Mean (SD) percentage change in DLQI score	64.8% (22.5%)	53.2% (47.7%)	73.1% (36.7%)	74.8% (30.4%)	54.9% (41.6%)
Frequency (n, %) with MCID reduction	11 (91.66%)	12 (75.0%)	17 (89.5%)	20 (90.9%)	21 (80.8%)
Frequency (n, % within subgroup) with DLQI MCID reduction and EASI-50	5 (50.0%)	7 (63.6%)	8 (80.0%)	12 (75.0%)	9 (56.3%)

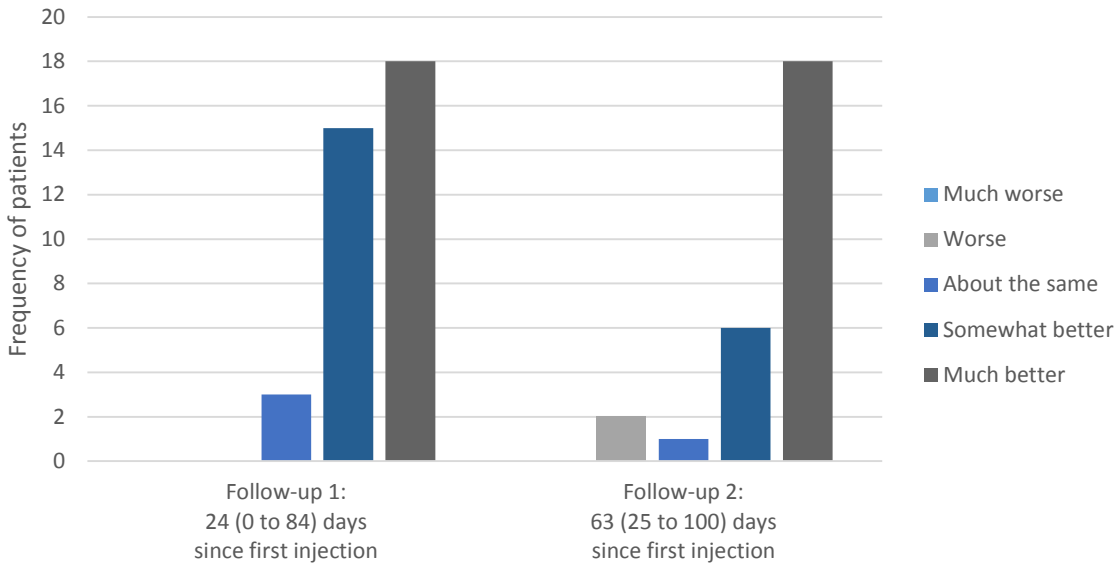
Note: Age was not reported for one patient.

3.4.4 Change in treatment response over time

The graphs below show the trend in clinician-rated treatment response over time. Please note, these data were available for fewer people at later follow-ups (36 at Follow-up 1, 27 at Follow-up 2, 18 at Follow-up 3 and 6 at Follow-up 4) thus graphs present only data for Follow-ups 1 and 2.

Figure 1 shows that the most common treatment response was ‘much better’, followed by ‘somewhat better’.

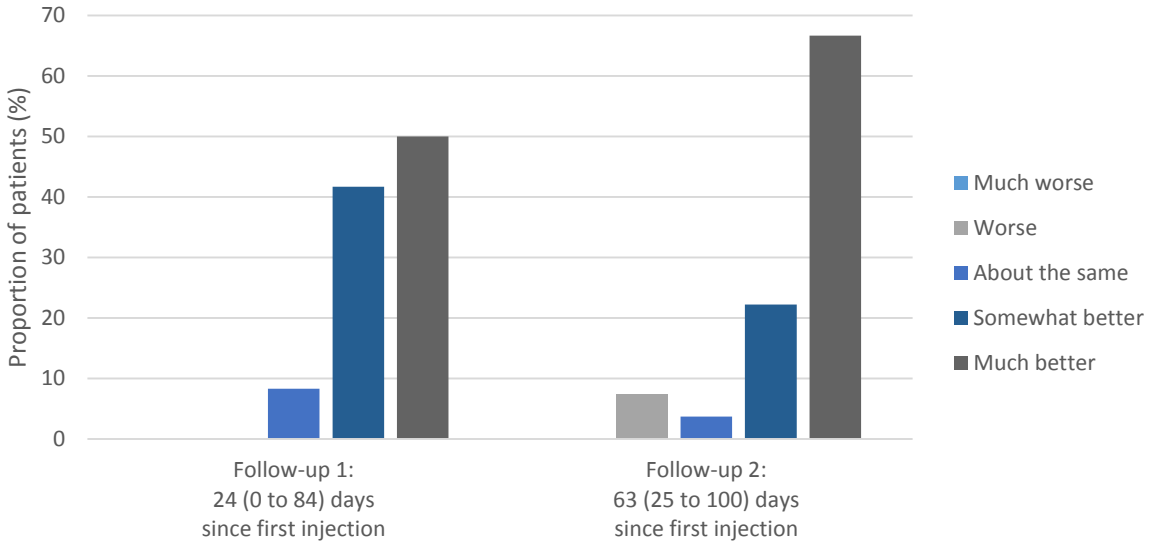
Figure 1: Clinician-rated treatment response at follow-ups one and two



Note: Days since first injection reported on the x axis reflect the mean (range) days between the first injection and clinician-reported treatment response, as reported by clinicians on data collection forms. There was some discrepancy across sites in the intervals between particular follow-ups.

Figure 2 shows the same data as a proportion of the total responses provided at that time point, and shows a similar pattern of results, with a greater proportion reporting a ‘much better’ response at the second follow-up than at the first.

Figure 2: The proportion of patients with each treatment response at each time point



Note: Days since first injection reported on the x axis reflect the mean (range) days between the first injection and clinician-reported treatment response, as reported by clinicians on data collection forms. There was some discrepancy across sites in the intervals between particular follow-ups.

Section 4: Summary

4.1 Key Findings

- Data were available for a total of 56 patients enrolled into the EAMS cohort, of which approximately two thirds were male, with an average age of 43 years.
- At 3 months, the majority of patients were rated as 'almost clear' according to the IGA scores, and two thirds of the patients for whom data were available had improved by at least two IGA categories. No clear patterns were observed in relation to age or immunosuppressant use.
- At 3 months, average EASI scores were at the lower end of the 'moderate disease' range of scores, with an average improvement of 19 points (63%). 73% patients for whom data were available showed a reduction of at least 50% in their EASI scores, and 79% showed at least a 6.6 point reduction, indicating they had made clinically significant improvements. It was observed that the reduction in EASI scores, and number of patients with clinically significant improvements was somewhat higher in patient without reported immunosuppressant use at enrolment, and in older adults. That said, the mean percentage change in EASI scores in older adults was lower than in the other age group.
- At 3 months, average DLQI scores indicated that AD had a moderate effect on the lives of patients, with an average improvement of 11 points (65%) since baseline. 88% patients showed at least a 4 point reduction, indicating the impact of AD on their quality of life had reduced to a clinically significant level. No clear patterns were observed in relation to age or immunosuppressant use.
- Two thirds of patients for whom data were available achieved both a reduction of at least 50% on EASI scores, and a minimally clinically important difference on the DLQI at both follow-ups.
- The pattern of results from the latest available time points and the three month follow-up was very similar.
- Clinicians most commonly rated the response to treatment as 'much better' across all patients and time points. The proportion of patients rated as demonstrating a 'much better' treatment response rose until Time 3, at which point a slight drop was observed. This finding should be interpreted with caution as it is likely due to small numbers of patients at Time 4.

References

1. Simpson *et al.* Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016. DOI: 10.1056/NEJMoa1610020.

2. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. British Journal of Dermatology. 2015 May 1;172(5):1353-7.

3. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean?. Journal of Investigative Dermatology. 2005 Oct 31;125(4):659-64.

4. Schram ME, Spuls PhI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minmal clinically important difference. European Journal of allergy and Clinical Immunology. 2012; 67: 99-106.

5. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. Dermatology. 2015; 230(1): 27-33.