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 Study Code: DUPILL09236	
STUDY REQUEST DATE: 08/02/2018	**TARGET DELIVERY DATE**: 01/04/2018
HEOR Researcher Author: Rajesh Rout	**Therapeutic area:** Immunology
Product Name: Dupilumab	**Disease:** Atopic Dermatitis
Protocol version number: 2.0 April 2018	

STUDY TYPE:

☒ **e: Analysis of Pre-existing Data (ie secondary use of data)**

SUB STUDY TYPE:

☒ **e3: Observational Studies based on secondary use of data**

Note: Best fit category selected, this is analysis of pre-existing data.

Sub study types e1,e2,e3 applicable to Study type e

PROGRAMME AIM(S):

To retrospectively analyse the treatment outcomes of patients with severe Atopic Dermatitis (AD) who were enrolled in the Early Access to Medicines Scheme (EAMS) for dupilumab, using quantitative and qualitative analysis. To provide supportive data to the Health Technology Appraisal (HTA) body should an appraisal consultation document (ACD) be issued after the first committee meeting expected in April 2018.

Use of EAMS outcome data to support the HTA submission

The medical rationale for this study is to further the understanding about the efficacy of dupilumab in a real world clinical setting. Dupilumab is currently being assessed by NICE through the single technology appraisal process. Sanofi will have the opportunity to provide supportive data to the institute in April 2018 should an appraisal consultation document (ACD) be issued after the first committee meeting. HTA bodies welcome the opportunity to review real world evidence to support clinical trial outcomes but it is very unusual to have these data for a product in the period directly after marketing authorisation. EAMS data collected in real-world clinical practice settings will be invaluable to the committee to help them in their deliberations.

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 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.

[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

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 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)**

POPULATION OF INTEREST

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**

Data Source(s) (for analyses of pre-existing data)**:**

☐ Clinical Trials ☐ Health Care Insurance Claims ☒ Electronic Medical Records ☒ Medical Charts

☐ Survey Data ☐ Cohorts or registries ☐ Other observational Data ☐ Published Data ☐ Others

Name of the database: Electronic medical records, charts and patient databases used for the treatment of patients in the NHS

Data selection criteria: EAMS sites. See inclusion and exclusion criteria above.

COMPARATORS OF INTEREST (based on reference treatments, accepted standard of care…..): N/A

OUTCOMES OF INTEREST (include definitions, key measurements, & evaluation criteria):
ENDPOINTS:

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)***

☐ *Please check if safety outcomes related to a Sanofi product intended to be analysed***

*** Safety follow-up was mandated by the MHRA, data was collected by Pharmacovigilance (PV) proactively until Marketing Authorisation (MA), this project will not collect safety follow-up data. Drug safety will review records after reporting.*

STUDY DESIGN & STATISTICAL ANALYSES PLAN:

Study Design
An observational, multi-centre, retrospective study conducted across EAMS centres in the UK. The study will analyse the treatment outcomes (as assessed by AD severity scores) of approximately n=160 eligible patients with severe AD, compared to baseline.

Number of Patients Planned
By the end of the EAMS period (27th September 2017), 244 patients were enrolled in the scheme. By the beginning of February 2018, approx. 160 patients will have completed 3 months of treatment with dupilumab. Note that as this data is required to respond to the ACD, as much data as possible will be collected before the deadline (01 April 2018).

Description of the Study Design / Methodology
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 (approx. n=160).

Baseline patient data is 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.

Duration of Study Participation
N/A. Collection of retrospective baseline data with no participant involvement. Patients will have received treatment with dupilumab for more than 3 months as per inclusion criteria.

Centre Identification
This is a retrospective analysis of data; all sites will have the opportunity to participate. Sites will be 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

Clinicians are responsible for obtaining local hospital R&D approval.

Assessment of feasibility at study sites

A feasibility assessment has been conducted to determine whether centres regularly record and have access to data on the primary outcomes of the study. 12 NHS centres throughout the UK enrolled patients into EAMS, one site is not eligible as the patient has received less than 3 months' treatment.

- Response to questionnaire: 8/11 sites (73%)
    - Of those who responded (n=8):
        - Willing to participate & capacity to complete data collection: 100%
        - Data routinely collected: EASI (88%), IGA (88%), DLQI (100%). POEM collected at some sites.
        - Written notes on response to treatment: 75%
        - R&D approval required for 0/8 sites

Patient Identification
This is 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 (approx. n=160).

Data Collection
Data collection and analysis will be conducted on behalf of Sanofi by the York Health Economics Consortium (YHEC), an independent healthcare research consultancy. YHEC will contact sites directly and will provide a paper/electronic CRF. Data will be collected in an anonymised format by members of the direct care team. Data will only be collected for patients who have consented at the start of EAMS. Data will be limited to the dataset outlined in this protocol. Once data has been collected, it will be sent in an anonoymised format (EAMS reference number), to YHEC, an independent healthcare research consultancy for data management, analysis and report generation.

Data Collected
Data collected at baseline (EAMS entry forms)
The following dataset was collected on each patient at baseline:

- Investigator Global Assessment score (IGA)
- Eczema Area Severity Index (EASI)
- Dermatology Life Quality Index (DLQI)
- Atopic Dermatitis History (severity, duration of disease, previous treatments (dose and duration)
- Past Medical History
- Past/Current medications
- Gender, Age, Weight, Height

Note: The first page of the enrolment form which contains centre name, clinician name and contact details, was removed before sending to the external agency (YHEC).

Data to be collected in the current analysis
Quantitative measures:

- Date of first injection
- Last EASI Score, date taken
- Last IGA Score, date taken
- Last DLQI Score, date taken
- Baseline POEM and last score with date taken (if recorded)

Qualitative measures:

- Notes on the patient response to treatment in the opinion of the clinician (as recorded on the patient notes, if applicable)

Only data stated in this protocol and that is explicitly available in the patient applications will be analysed. No new data will be inferred or generated through prospective methodologies.

Transfer & Data Management
Once data has been collected into the CRF, a copy will be transferred to YHEC for analysis and reporting. A copy of the completed CRF will remain at the centre. Data received by YHEC for data management will be checked for patient eligibility, accuracy and completeness using visual and programmed validation checks. Data queries will be raised with each centre and resolution and any corrections will be made by reference to patient medical records by the appropriate healthcare professional. All forms will be kept in a locked cupboard when not in use by the study team. Entry to the study electronic data capture system (where used) and study database will be restricted (by password protection) to only those members of staff directly involved with the study.

Monitoring and Site Data Quality Control
A 'back-to-back' approach will be used for data monitoring. This process will involve a YHEC staff member repeating data on CRFs to a site staff-member with access to patient records by telephone. The latter will check the data against the patient record. A total of 20% of the data, i.e. 32 records will be checked in this way.

Ethical considerations
Consideration was given to whether this study would be considered 'research' prior to study start (February 2018). This was confirmed using the tool on the HRA website which takes answers to the following questions into consideration:

Is your study research?

- Are the participants in your study randomised to different groups? 'No'
- Does your study protocol demand changing treatment/patient care from accepted standards for any of the patients involved? 'No'
- Are your findings going to be generalisable? 'No'

Your study would NOT be considered Research by the NHS.

Does your study require HRA approval?

- Is your study research? 'No'
  which indicates that you do not need NHS approval.

You have answered 'No' to the question "Is your study research" which indicates that you do not need NHS approval.

Tool: https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/

This was confirmed in an email to the HRA in February 2018 and the study subsequently started. **Following a query by a site in April 2018, the HRA stated that this would be considered as 'research', therefore, the IRAS application is being made after the start of data collection.**

No patient identifiable information will be collected; therefore no application is required to the Confidentiality Advisory Group (CAG). Clinicians are responsible for obtaining local hospital R&D approval if required.

Statistical considerations
The objective is to collect data on the outcomes of patients treated with dupilumab through EAMS for more than 3 months (EASI, IGA, DLQI) and compare results with baseline scores. No power calculations have been carried out for this study, data from the available cohort that can be collected within the deadline will be collected.

Analysis

The analysis will be performed by YHEC. The analysis will include descriptive statistics of the follow-up dermatitis scores. See the Statistical Analysis Plan (SAP).

Reporting
The external agency will generate a report following completion of the analysis.

Pharmacovigilance
This is no requirement for individual patient or subject data collection as part of this pre-existing data analysis. The service provider will provide the final study report to Sanofi to review and/or identify any safety concerns within 1 working day of its completion.

The service provider is, however, reminded of their pharmacovigilance obligations to report any safety information or technical complaints which they become aware to Sanofi Drug Safety or Quality within 1 working day.

Responsibilities
Responsibilities of the Investigators
The Investigator will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator's responsibility to:

- Ensure that the information reported in the CRF is precise and accurate and complete according to the source data
- Ensure that the information reported in the CRF and transferred remains anonymised

Responsibilities of YHEC
YHEC is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

YHEC is responsible for:

- Local submission(s) and complying with data protection rules
- Management of centres
- Overall study management
- Collating and validating data
- Data analysis
- Reporting of results

Data Protection
The patient data shall be treated in compliance with all local applicable laws and regulations. Patients gave their permission for data to be used by Sanofi and a suitable third party at enrolment into EAMS. Sanofi hold evidence of such consent. Original signed consent forms are held at site (for data privacy reasons).

Insurance
Insurance is not required as this is a non-interventional study with no risk of harm to participants. This is a retrospective analysis of baseline data. The project is not seeking patient consent (already obtained), does not require EC approval and anonymised data will be obtained direct from the patients care team.

Ownership and Use of Data and Study Results
No use of the data collected for the study will be possible without the authorisation of Sanofi (see contract).

Publications
It is anticipated that the study results will provide supportive data to the HTA body should an appraisal consultation document (ACD) be issued after the first committee meeting expected in April 2018. Sanofi have obtained consent from the patient to publish data, as long as they are not identifiable in any way.

STUDY MILESTONES/TIMELINES :

- Data collection: March 2018
- Start of data analysis: 01 April 2018
- Final report by YHEC: 15 April 2018

COMMUNICATION/PUBLICATION PLAN: HTA submission: April 2018

APPENDIX 1: STUDY MEASURES OPTIONS

Burden of Disease: N/A

☐ disease (frequency/prevalence/incidence);

☐ comorbidity;

☐ resource utilization;

☐ disease progression or outcomes;

☐ disease stages /severity;

☐ others, please specify:

Treatment Patterns:

☐ duration;

☐ dosage;

☐ strength;

☐ routes of administration (injection, IV, oral);

☐ sequence of treatment;

☐ treatment switch;

☐ discontinuation;

☐ medication possession ratio;

☐ compliance, persistence;

☐ concomitant treatments;

☐ hospital vs. ambulatory, specialty care.

☐ others, please specify:

Clinical Outcomes: NA

☒ treatment response (e.g., A1C, blood pressure, lipid, body weight, CV events, survival),

☐ hospitalization,

☐ additional biomarkers.

☐ others, please specify:

Economic Outcomes (cost & utilization): N/A

☐ medical and pharmacy utilization,

☐ hospital admission, readmission, length of hospital stay, inpatient costs, frequency of hospital admissions,

☐ outpatient and ER visits & cost,

☐ Indirect Costs, Productivity, Absenteeism/ Presenteeism,

☐ Short Term Disability, Long Term Disability.

☐ others, please specify:

Patient Reported Outcomes: N/A

☒ QoL,

☐ treatment satisfaction,

☒ symptom measures,

☐ utility measures,

☐ functional measures,

☐ impairment measures,

☐ cognitive measures,

☐ familial/ collateral respondents.

☐ others, please specify:

APPENDIX 2: Statistical Analysis Plan (SAP)

1. Data Processing

Data will be entered into an Excel template with predefined fields by a single researcher. Where appropriate, for continuous variables conditional formatting will be used to highlight unexpected entries (i.e. entries outside the possible range of values), and for categorical inputs, drop-down boxes will be used to ensure consistency of input. The following variables will be captured:

- Patient ID;
- Atopic dermatitis (AD) scores: (at intervals by patient follow-up date)
    - EASI score (extent, 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 will be provided on patient response to treatment as recorded in the patient notes. These notes will be mapped to a 5 point Likert scale by the clinician.

Where handwritten notes are illegible, forms will be returned to the client securely for clarification.

The following data was collected at baseline (in enrolment forms, for the purpose of assessing eligibility for EAMS):

- Patient demographics:
    - Age (years);
    - Sex;
    - Height (cm);
    - Weight (kg);
- 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);
    - Monoclonal antibodies (e.g. ustekinumab).

Where missing or clearly erroneous (i.e. age implausible given other variables), a proxy age will be calculated using the birth date and consent date.

For weight and height, decimals will be rounded to the nearest whole number and in any cases where the measurements are reported in alternative units, units will be converted to kg and cm.

Ratings of IGA of '5' are 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 will be recategorised as '4'. Ratings across categories (e.g. a rating of 3 to 4) are assumed to reflect a severity that the clinician did not persistently consider in the higher category, and thus will be recategorised at the lower score.

A second researcher will review the data for unexpected entries and perform detailed checking of 10% entries.

2. Data Analysis

The data will then be imported into SPSS for analysis. The analysis will include descriptive statistics of the sample characteristics, dermatitis scores, as well as past and current AD treatments (treatments recorded at baseline). 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, respectively) will be calculated.

- Patients will be categorised into those who achieved a $\geq$4-point improvement in DLQI and EASI-50 scores (at 3 months and then at full available follow up-period).

Age will then be categorised into the following groups:

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

Observation period will be calculated as the difference in time between the dates of the first and follow-up CRF in weeks for each patient. These will be summarised to provide:

- Mean (weeks)
- Standard Error
- Standard Deviation
- Range

Dermatitis scores will be 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[1]):
  - 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 [2]):
  - 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.
- POEM scores (as per Charman et al., 2013[3]):
  - Clear or almost clear = 0 to 2;
  - Mild eczema = 3 to 7;
  - Moderate eczema = 8 to 16;
  - Severe eczema = 17 to 24;
  - Very severe = 25 to 28.

For categorical variables (e.g. sex, past and current treatments), frequencies and proportions will be calculated.

If required, a retrospective power analysis may be calculated based on the proportion of patients achieving the Minimally Clinically Important Difference (MCID) in EASI/DLQI/POEM score and/or a >4-point improvement on both the DLQI and EASI-50 scores at 3 months (compared to the proportion of patients achieving < on these scales).

Analysis of demographics (age and sex) and categorised dermatitis severity scores (IGA, EASI) will be reported for the sample as a whole, and split by past immunosuppressant use. This will first be 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 immunosuppressant.

The following analyses will be conducted to compare current with baseline data:

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

All the above will be reported for the full follow-up period and then specifically for patients with a complete record at 3 months. Patient response to treatment over time will be reported graphically. Height and weight variables will not be analysed.

The clinicians' rating of patient of treatment response, and published minimal clinically important differences (MCID) for EASI and POEM[4], as well as the DLQI[5], will be used to provide a qualitative interpretation of change in patient scores from baseline.

[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] Charman CR, Venn AJ, Ravenscroft JC, Williams HC. British Journal of Dermatology. 2013; 169(6): 1326-1332).
[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.

Analyses will be sense-checked and reviewed to check for accurate transcription by a second researcher.

[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.