Statistical Analysis Plan for Study M19-850

An Open-Label Treatment Extension Study for the Treatment of Adult Subjects with Moderate to Severe Atopic Dermatitis Who Completed Treatment in Study M16-046

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Version 5.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for upadacitinib Study Protocol M19-850, A Phase 3b, open-label treatment extension study of upadacitinib for the treatment of adult subjects with moderate to severe atopic dermatitis who completed treatment in Study M16-046.

Study M19-850 examines the long-term safety, tolerability and efficacy of upadacitinib in adult subjects with moderate to severe atopic dermatitis who successfully completed treatment in Study M16-046.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The objective of this study is to assess the long-term safety, tolerability and efficacy of upadacitinib in adult subjects with moderate to severe AD who successfully completed treatment in Study M16-046.

2.2 Study Design Overview

This is a Phase 3b, single arm, open-label extension (OLE) study for adults (18 – 75 years of age at entry into Study M16-046) with moderate to severe AD who have successfully completed treatment in Study M16-046. These subjects should be determined to be eligible to continue treatment with upadacitinib by the Principal Investigator during the

Baseline visit of this OLE study. The Baseline visit for this study will be the Week 24 visit of Study M16-046.

The study is comprised of a Baseline visit (Week 24 visit of Study M16-046), a 52-week open-label treatment period, and an 84-Week End-of-Study Follow-Up Visit (or phone call if a visit is not possible 30 days after the last dose of upadacitinib). End-of-Study Follow-Up visits are only applicable for the following countries and regions: Germany, France, Finland, Netherlands, Norway, Taiwan, Croatia, Poland, Czech Republic, and Hungary. The 30-day follow-up visit is done to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs is required. These subjects will be considered as having completed the study. Subjects, who are eligible to enroll in the OLE study, will receive daily oral doses of upadacitinib 30 mg from the Baseline visit up to the Week 52 visit. The schematic of the study is shown in Figure 1.

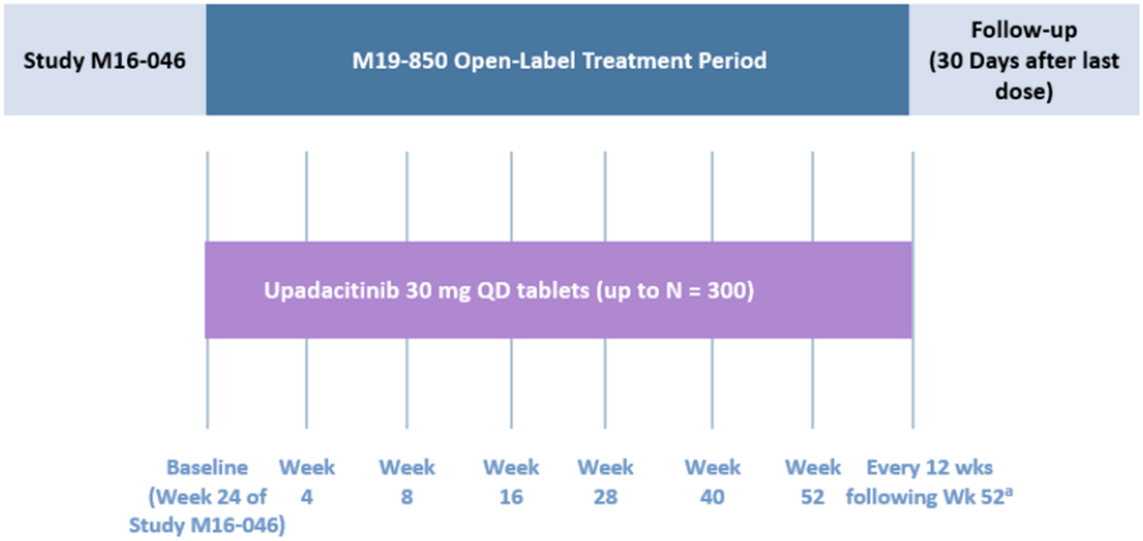
Safety and efficacy assessments will be performed through Week 52 for all sites, and additional safety assessments will be performed every 12 weeks after Week 52 up to Week 136 for sites in the following countries and regions: Germany, France, Finland, Netherlands, Norway, Taiwan, Croatia, Poland, Czech Republic, and Hungary.

See Section 5.0 of the protocol for information regarding eligibility criteria.

An interim analysis will occur after all ongoing subjects have completed the Week 16 visit. The schematic of the study is shown in Figure 1.

The Final database lock will take place after all subjects complete the study.

Figure 1. Study Schematic



QD=once daily

a. Efficacy evaluations will not be performed after Week 52.

2.3 Treatment Assignment and Blinding

All subject enrolled to M19-850 will receive open label upadacitinib 30 mg QD throughout the study.

The type and amount of kits dispensed will be managed by the Interactive Response Technology (IRT).

2.4 Sample Size Determination

Approximately 600 subjects who complete treatment in Study M16-046 will roll over in this open label treatment extension study. The sample size is determined by the expected rate of completion of Study M16-046 and subject consent for the extension.

3.0 Endpoints

3.1 Primary Endpoints

There is no primary efficacy endpoint for this study.

The primary safety endpoints are:

- Treatment emergent adverse events (TEAEs);
- Serious adverse events (SAEs);
- Adverse events of special interest (AESI);
- AEs leading to discontinuation of study drug;
- Vital signs, laboratory tests, and physical examination findings

3.2 Secondary Endpoints

There is no secondary efficacy endpoint for this study.

3.3 Other Efficacy Endpoints

The following efficacy endpoints will be assessed at all visits through Week 52. Baseline refers to the Baseline value in Study M16-046. All endpoints are defined relative to the Baseline values in Study M16-046.

- Change and percent Change from Baseline in EASI;
- Change and percent change from Baseline in Worst Pruritus Numerical Rating Scale (NRS);
- Proportion of subjects achieving EASI 75/90/100;
- Change from Baseline in body surface area (BSA);
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS $\geq$ 4 from Baseline among subjects who had Worst Pruritus NRS $\geq$ 4 at Baseline;
- Proportion of subjects achieving 75% reduction in EASI in the head and neck body region from Baseline;

- Proportion of subjects achieving 75% reduction in EASI in each body region (other than head and neck) from Baseline;
- Proportion of subjects achieving 75% reduction in EASI in the head and neck body region among subjects who received dupilumab in Study M16-046 and did not achieve 75% reduction in EASI in the head and neck body region at Week 24 of Study M16-046;
- Proportion of subjects achieving 75%/90%/100% reduction in EASI (EASI 75/90/100) among subjects who received dupilumab in Study M16-046 and did not achieve EASI 75 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 90/100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 90 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 100 at Week 24 of Study M16-046;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS reduction ≥ 4 among subjects who had Worst Pruritus NRS ≥ 4 at Baseline, received dupilumab in Study M16-046 and did not achieve Worst Pruritus NRS reduction ≥ 4 at Week 24 of Study M16-046.

3.4 Safety Endpoints

The safety endpoints are described in Section 3.1.

4.0 Analysis Populations

Significant non-compliance was identified at a site. As a result of this finding, subjects enrolled in this site will not be included in any analysis population and data collected from this site will not be included in any analysis.

The following populations will be used for the analyses.

The Intent-to-Treat (ITT) Population consists of all enrolled subjects who receive at least one dose of study drug in the study and will be used for the efficacy analyses.

The Safety Population is the same as the ITT Population for this study. This population will be used to provide a comprehensive summary of safety.

5.0 Subject Disposition

The total number of subjects who were treated will be summarized.

The number of subjects for each of the following categories will be summarized by treatment group randomized in M16-046 in the ITT Population:

- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug (all reasons and primary reason);
- Subjects who completed the study;

Number and percentage of subjects who discontinued study drug will be summarized by reason (primary reason and all reasons). Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations.

6.0 Study Drug Duration and Compliance

Study Drug Duration (in Days):

Summary of study drug duration and study drug compliance will be provided in M19-850 for the Safety Population during the entire treatment period. Study drug duration (days) will be summarized using the number of subjects, mean, standard deviation, minimum, median and maximum for each treatment group.

- Duration of upadacitinib is defined for each subject as last dose date of upadacitinib minus first dose date of upadacitinib +1,

In addition, the number and percentage of subjects exposed to upadacitinib will be summarized for the following categories of exposure duration for the Safety Population starting from the first dose of upadacitinib in M16-046 or M19-850:

- ≥ 4 weeks
- ≥ 12 weeks
- ≥ 24 weeks
- ≥ 36 weeks
- ≥ 48 weeks
- ≥ 52 weeks
- ≥ 64 weeks
- ≥ 76 weeks
- ≥ 88 weeks
- ≥ 100 weeks
- ≥ 112 weeks
- ≥ 124 weeks
- ≥ 136 weeks
- ≥ 148 weeks
- ≥ 160 weeks

Compliance:

Treatment compliance will be summarized in the Safety Population for the entire treatment period.

Upadacitinib compliance for an individual subject is defined as the number of upadacitinib actually taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) by the subject divided by the number of tablets planned to be taken by the subject during the study.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, and medical history will be summarized for ITT overall and by M16-046 treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum). Prior and concomitant medications will be summarized for the Safety Population overall and by M16-046 treatment group.

7.1 Demographics and Baseline Characteristics

Subject Demographics

The following demographic and Baseline parameters will be summarized.

Unless otherwise specified, the baseline below refers to the baseline of Study M16-046.

Subject Demographics

- Sex (male, female)
- Age (years), defined as the number of years from date of birth to date of first drug
- Age categories (< 40, ≥ 40 to < 65, ≥ 65 years).
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multi Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body weight (kg)

General Baseline Characteristics at the Entry of Study M16-046 and Study M19-850

- EASI (Eczema Area and Severity Index)
- BSA (Body Surface Area) with Atopic Dermatitis

- Worst Pruritus NRS
- Daily Worst Pruritus NRS (Entry of Study M16-046 only)
- IGA categories (< 3 or missing, 3, 4) (Entry of Study M16-046 only)

Atopic Dermatitis History

- Duration of Atopic Dermatitis since diagnosis (years)
- Duration of Atopic Dermatitis between symptoms and diagnosis (years)

Nicotine and Alcohol Use

- Smoking history (Unknown, Never, Current, Former)
- Alcohol History (Unknown, Never, Current, Former)

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Medical history will be summarized in the ITT Population.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug of Study M16-046. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug of Study M19-850 and continued to

be taken after the first dose of study drug of Study M19-850 or any medication that started on or after the date of the first dose of study drug of Study M19-850, but not after the date of the last dose of study drug of Study M19-850. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

Prior and concomitant medications will be summarized in the Safety Population.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Since M19-850 does not have primary or secondary efficacy endpoints, so there is no handling of potential intercurrent events for them.

9.0 Efficacy Analyses

9.1 General Considerations

An Interim Analysis will be performed after all ongoing subjects have completed the Week 16 visit. The Final database lock will be performed at the end of study.

Efficacy variables will be summarized in the Study M19-850 ITT Population at each visit of Study M16-046 and Study M19-850, unless otherwise specified. No statistical testing will be performed.

A subject's M16-046 Baseline is defined as the last non-missing observation on or before their first dose of study drug in M16-046. For randomized but not treated subjects, the Baseline value will be the last non-missing measurement recorded prior to randomization. All efficacy endpoints defined below are relative to the M16-046 Baseline unless otherwise specified.

Efficacy assessments for ITT Population will be presented for the following three groups at each visit:

- subjects originally randomized to dupilumab in Study M16-046

- subjects originally randomized to upadacitinib in Study M16-046
- ITT Population (only applicable at visits of Study M19-850)

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum, 25th and 75th percentiles, as well as the 95% confidence intervals (CIs) of the mean values. Categorical variables will be summarized by counts and percentages, as well as the 95% CIs of the percentages.

The Observed Cases (OC) approach as defined in Section 9.2 will be used for all efficacy variables.

Analysis of Categorical Variables

For ITT Population, frequencies and percentages will be summarized along with 95% confidence interval (CI) based on normal approximation.

OC will be the only approach for categorical endpoints (Section 9.2).

Analysis of Continuous Variables

For ITT Population, the raw values at each visit and Baseline, change from Baseline/percent change from Baseline will be presented for the three treatment groups mentioned in this Section who have both Baseline and post-baseline visit values. The mean, 95% confidence interval, standard error, Min, Q1, median, Q3 and Max will be summarized.

9.2 Handling of Missing Data

Missing data will be handled using the following methods for the efficacy analyses:

- Observed Cases (OC): The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit. OC will exclude values after a subject prematurely discontinue from study drug + 1 days.

OC will be the only imputation method for all the efficacy endpoints.

9.3 Primary Efficacy Endpoints and Analyses

9.3.1 Primary Efficacy Endpoints

There is no primary efficacy endpoint for this study.

9.3.2 Main Analysis of Primary Efficacy Endpoints

This section is not applicable since there is no primary endpoint in this study.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoints

This section is not applicable since there is no primary endpoint in this study.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

There is no secondary efficacy endpoint for this study.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

This section is not applicable since there is no secondary endpoint in this study.

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoints

This section is not applicable since there is no secondary endpoint in this study.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

This section is not applicable since there is no secondary endpoint in this study.

9.5 Additional Efficacy Analyses

Other efficacy endpoints are listed in Section 3.3. The analysis detail is specified in Section 9.1.

The following endpoints will be summarized only at the visits of Study M18-850.

- Proportion of subjects achieving 75% reduction in EASI in the head and neck body region among subjects who received dupilumab in Study M16-046 and did not achieve 75% reduction in EASI in the head and neck body region at Week 24 of Study M16-046;
- Proportion of subjects achieving 75%/90%/100% reduction in EASI (EASI 75/90/100) among subjects who received dupilumab in Study M16-046 and did not achieve EASI 75 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 90/100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 90 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 100 at Week 24 of Study M16-046;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS reduction ≥ 4 among subjects who had Worst Pruritus NRS ≥ 4 at Baseline, received dupilumab in Study M16-046 and did not achieve Worst Pruritus NRS reduction ≥ 4 at Week 24 of Study M16-046.

Missing data will be imputed as specified in Section 9.2.

9.6 Efficacy Subgroup Analyses

There will be no efficacy subgroup analyses in this study.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Population. Safety summaries will include data collected from the first dose of updacitinib in Study M16-046 or Study M19-850, whichever is earlier.

All the safety related endpoints will be summarized for the following three groups, unless otherwise specified:

- Subjects originally randomized to dupilumab in Study M16-046 and continued in Study M19-850
- Subjects originally randomized to upadacitinib in Study M16-046 and continued in Study M19-850
- All the subjects dosed in Study M19-850

For laboratory and vital sign tables, only the first two groups will be included.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any adverse events that begin or worsen in severity after initiation of upadacitinib during Study M16-046 or

Study M19-850 through 30 days following the last dose of upadacitinib. If an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event is not treatment-emergent (e.g., the event end date is prior to the study drug start date). Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. All treatment-emergent AEs in the Safety Population will be summarized during the administration of upadacitinib in Study M16-046 and/or Study M19-850, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs as well as exposure-adjusted number of events will be summarized.

10.2.2 Adverse Event Overview

An overview of TEAEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following TEAE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE (Grade 3 and above according to NCI CTCAE version 5)
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
  - All deaths will be summarized:
- Deaths occurring ≤ 30 days after last dose of study drug
- Deaths occurring > 30 days after last dose of study drug.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by SOC and PT and maximum toxicity; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest toxicity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the study treatment group.

The following summaries of adverse events will be generated:

- All TEAEs
- Treatment-emergent serious adverse events
- Treatment-emergent severe adverse events
- TEAEs related to study drug according to the investigator
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Exposure-adjusted number of TEAEs per 100 patient-years will be provided, where number of TEAEs per 100 patient-years of exposure are defined as the number of TEAEs divided by the total exposure in 100 patient-years. These will be presented for the following TEAE categories.

- Any TEAE
- Any treatment-emergent SAE
- Any TEAE leading to discontinuations of study drug

- Any severe TEAE
- Any TEAE related to study drug according to the investigator
- Any treatment-emergent SAE related to study drug according to the investigator
- Any TEAE leading to death

Note that one event per preferred term per day per subject will be counted in the calculation of the number of TEAEs (i.e., a preferred term will not be counted twice on the same day for the same subject). See the calculation method below:

- 100 * (Number of TEAEs)/(Total Patient Years)

where total patient years is defined as the sum of the study drug duration (defined in Section 6.0) + 1 days of all subjects normalized by 365.25, and rounded to 1 decimal place.

10.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

10.2.6 Adverse Events of Special Interest

The AESI categories will be identified by the following search criteria per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs) specified in Appendix B.

Overview and exposure-adjusted event rates per 100 patient-years of Treatment-emergent Adverse events of special interest will be provided.

Treatment-emergent Adverse events of special interest will be summarized by SOC and PT and listing format. Additionally, AESI rates per 100 patient years of study drug exposure using SOC by PT will be provided for each treatment group.

Information on the extent of herpes zoster infection and acne will be summarized as collected in the respective AE form.

10.2.7 Listing of Adverse Events

The following additional summaries will be provided for treatment-emergent adverse events, unless otherwise specified.

- List of subject numbers associated with each PT for TEAEs.
- List of subject numbers associated with each PT for TEAEs related to study drug according to the investigator
- Listing of treatment-emergent SAEs.
- Listing of TEAEs leading to discontinuation of study drug.
- Listing of all deaths.
- Listing of treatment-emergent AESIs.

10.2.8 Acne Adverse Events

The investigator-identified acne AEs will be summarized by involvement, morphology, and predisposing factors.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. For the assessments of laboratory data, values collected more than 30 days after the last dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Table 1. List of Laboratory Variables

Clinical Laboratory Tests		
Hematology	**Clinical Chemistry**	**Other Tests**
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count	BUN Creatinine Total bilirubin INR (reflex only)[a] Albumin ALT AST Alkaline phosphatase CPK Sodium Potassium Bicarbonate/CO2 Chloride Calcium Inorganic phosphorus Uric acid Total protein Glucose Cholesterol LDL-C HDL-C Triglycerides	Central Lab Tests: Serum pregnancy (beta human chorionic gonadotropin [bHCG]) test Hepatitis B virus deoxyribonucleic acid polymerase chain reaction (HBV DNA PCR [Per Toxicity Management Guidelines only]) QuantiFERON-TB Gold High-sensitivity C-reactive protein (hsCRP) Local Lab Tests: Urine pregnancy test PPD test/T-SPOT TB
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO^2 = carbon dioxide; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HDL-C = high-density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PCR = polymerase chain reaction; PPD = purified protein derivative (tuberculin); RBC = red blood cell; TB = tuberculosis; WBC = white blood cell

a. INR will only be measured if ALT and/or AST > 3 × upper limit of normal (ULN).

Each laboratory variable will be summarized for the following time points:

- Subjects originally randomized to dupilumab in Study M16-046 and continued in Study M19-850: All post-baseline visits in M19-850. The Baseline for this group is defined as the last non-missing observation on or before their first dose of study drug in M19-850.

- Subjects originally randomized to upadacitinib in Study M16-046 and continued in Study M19-850: All post-baseline visits in M16-046 and M19-850. The Baseline for this group is defined as the last non-missing observation on or before their first dose of study drug in M16-046.

The summary includes the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit mentioned above will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline.

Changes in laboratory parameters will be tabulated using shift tables by NCI CTC criteria version 4.03. A shift table from baseline either to the worse value (based on NCI CTC criteria) during treatment or to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

Laboratory abnormalities meeting CTC criteria grade 3 and 4 will be summarized.

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria during the administration of upadacitinib in Study M16-046 and Study M19-850 (Appendix C). For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria.

According to FDA's Guidance for Industry Drug-Induced Liver Injury: Premarketing clinical evaluation (July 2009), when aminotransferase (AT) abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation > 2 × ULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol

hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI. For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest should be presented:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- TBL ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

10.4 Analysis of Vital Signs

Each vital sign variable will be summarized for the following time points:

- Subjects originally randomized to dupilumab in Study M16-046 and continued in Study M19-850: All post-baseline visits in M19-850. The Baseline for this group is defined as the last non-missing observation on or before their first dose of study drug in M19-850.
- Subjects originally randomized to upadacitinib in Study M16-046 and continued in Study M19-850: All post-baseline visits in M16-046 and M19-850. The Baseline for this group is defined as the last non-missing observation on or before their first dose of study drug in M16-046.

The summary includes non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit mentioned above will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria during the administration of upadacitinib in Study M16-046 and Study M19-850 (Appendix C). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

10.5 Safety Subgroup Analyses

There are no planned subgroup analyses for safety.

10.6 Other Safety Analyses

There are no other safety analyses planned.

11.0 Other Analyses

There are no other analyses.

12.0 Interim Analyses

One interim analysis is planned for this study, which will take place after all ongoing subjects finish the Week 16 Visit with cutoff date as 09MAR2021.

12.1 Data Monitoring Committee

There is no Data Monitoring Committee for this open-label study.

13.0 Overall Type-I Error Control

14.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	26 February 2020	Original version
2.0	09 April 2021	Added Section 8.0 following new SAP template. Section 2.2: Updated Figure of study design to incorporate the protocol amendment. Also added description about extending the study duration of certain countries and regions. Section 5.0: Removed the statement of summarizing screen failures since there will be no screening for this study. Also removed the statement of summarizing subjects with at least one dose of study drug. Because 'having at least one dose of study drug' is already the definition of ITT Population. Section 6.0: Added more categories of exposure duration following the protocol amendment of extending the dosing duration. Section 7.1. Removed baseline summary of Daily worst pruritus Numerical Rating Scale (NRS) as this is not applicable for M19-850 Baseline. Section 7.2: Clarified that Medical History will be summarized based on ITT Population. Section 7.3: Clarified that Prior and Concomitant Medication will be summarized based on Safety Population. Section 9.1 and Section 12.0: State that we would conduct an Interim Week 16 Lock. Section 9.2: Clarified that OC will exclude values after a subject prematurely discontinue from study +1 days. Section 10.3: Clarified the Baseline definition of lab analysis, as well as the visits for analysis. Section 10.4: Clarified the Baseline definition of vital sign analysis, as well as the visits for analysis. Appendix A: Added 'Subject with Deviation Related to COVID-19 Pandemic' to be consistent with M16-046. Appendix F: Added this section to include the activity schedule.

Table 2. SAP Version History Summary (Continued)

Version	Date	Summary
3.0	14 April 2021	Section 10.2.7: Deleted 'listings of pre-treatment AE' as they are not needed for this open label extension study.
4.0	21 June 2021	Section 5.0: Clarified that subjects who were rescued in the study will not be summarized. Section 6.0: Clarified that study drug duration and compliance will be summarized based on Safety Population. Section 7.1: Modified the demographics section to be consistent with eCRF design. Section 7.1: Added the Worst Pruritus NRS summary for both M16-046 and M19-850 Baseline, as well as Daily NRS for M16-046 Baseline. Section 10.2.3: Clarified that the TEAE will be summarized by SOC and PT and maximum toxicity instead of by maximum toxicity and SOC and PT. Appendix C: Updated the PCI criteria to be consistent with M16-046.
5.0	01 August 2023	Section 4.0: Added statement about excluding a site from all analyses due to non-compliance.

15.0 References

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.
- Subject with deviation related to COVID-19 Pandemic

Appendix B. Definition of Adverse Events of Special Interest

AEs of Special Interest (AESI) will be identified by the following CMQ, SMQ, and other search criteria:

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection excluding tuberculosis and herpes zoster	CMQ		"Opportunistic Infection excluding tuberculosis and herpes zoster"
Malignancy	SMQ		"Malignant Tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ/CMQ	SMQ Broad	Skin Malignant tumours (Broad SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			Malignancy Narrow SMQ and removing NMSC output
Lymphoma	SMQ		"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders"
Adjudicated Gastrointestinal Perforations	Adjudicated events identified by the "Gastrointestinal Perforation" SMQ Narrow search		
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia (Veliparib Product Specific)"
Herpes Zoster	CMQ		"Herpes Zoster"
Creatine Phosphokinase (CPK Elevation)	PT		Search only for the PT of "Blood creatine phosphokinase increased"
Renal Dysfunction	SMQ	Narrow	"Acute Renal Failure"
Active Tuberculosis	CMQ		"Active Tuberculosis"

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Adjudicated cardiovascular events[a]	Output from CAC		
MACE*			
Cardiovascular Death			
Non-fatal Myocardial Infarction			
Non-fatal Stroke			
Other Adjudicated Cardiovascular Events			
Undetermined/Unknown Cause of Deaths			
Adjudicated Thrombotic Events	Output from CAC		
VTE**			
Deep Vein Thrombosis			
Pulmonary Embolism			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

CAC = Cardiovascular Adjudication Committee; CMQ = company MedDRA query; PT = preferred term; SMQ = standard MedDRA query

* MACE: Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** VTE: Venous thromboembolic events, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non-fatal).

a. Reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner.

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table C-1 and Table C-2, and the PCI criteria for vital sign findings are described in Table C-3.

Table C-1. Criteria for Potentially Clinically Important Hematology Values

			Definition of Potentially Clinically Important
Hematology Variables	**Grade**	**Units**	**Very Low**
Hemoglobin	3	g/L	< 80.0
Platelets count	3	10^9/L	25.0 - < 50.0
	4	10^9/L	< 25.0
Leukocytes	3	10^9/L	1.0 - < 2.0
	4	10^9/L	< 1.0
Neutrophils	3	10^9/L	0.5 - < 1.0
	4	10^9/L	< 0.5
Lymphocytes	3	10^9/L	0.2 - < 0.5
	4	10^9/L	< 0.2

Note: A post-baseline value must be more extreme than the baseline value in CTC grade to be considered a potentially clinically important finding.

Table C-2. Criteria for Potentially Clinically Important Chemistry Values

Chemistry Variables	Grade	Units	Definition of Potentially Clinically Important	
			Very Low	Very High
ALP	3	U/L		> 5.0 × ULN – 20.0 × ULN
	4	U/L		> 20.0 × ULN
SGOT/AST	3	U/L		> 5.0 × ULN – 20.0 × ULN
	4	U/L		> 20.0 × ULN
SGPT/ALT	3	U/L		> 5.0 × ULN – 20.0 × ULN
	4	U/L		> 20.0 × ULN
Albumin	3	g/L	< 20	
Glucose	3	mmol/L	1.7 - < 2.2	> 13.9 – 27.8
	4	mmol/L	< 1.7	> 27.8
Triglycerides	3	mmol/L		> 5.7 – 11.4
	4	mmol/L		> 11.4
Creatinine	3	umol/L		> 3.0 × ULN – 6.0 × ULN or > 3.0 × Baseline
	4	mcmol/L		> 6.0 × ULN
Potassium	3	mmol/L	2.5 - < 3.0	> 6.0 – 7.0
	4	mmol/L	< 2.5	> 7.0
Calcium	3	mmol/L	1.5 - < 1.75	> 3.1 – 3.4
	4	mmol/L	< 1.5	> 3.4
Sodium	3	mmol/L	120 - < 130	155 - <160
	4	mmol/L	< 120	> 160
Phosphate	3	mmol/L	0.3 - < 0.6	
	4	mmol/L	< 0.3	
CPK	3	U/L		> 5.0 × ULN – 10.0 × ULN
	4	U/L		> 10.0 × ULN
Total Cholesterol	3	mmol/L		10.34 <- 12.92
	4	mmol/L		> 12.92

Note: A post-baseline value must be more extreme than the baseline value with at least one CTC grade of worsening to be considered a potentially clinically important finding.

Table C-3. Criteria for Potentially Clinically Important Vital Sign Values

Vital Signs	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic Blood Pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse (bpm)	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Weight	Low	> 7% increase from baseline
	High	> 7% decrease from baseline

Appendix D. EASI Scoring Algorithm

An EASI score is a tool used to measure the extent (area) and severity of atopic eczema (Eczema Area and Severity Index). EASI score does not include a grade for dryness or scaling.

Assignments for the following body regions are as follows:

- Head and Neck
- Trunk: include with the lower extremities
- Upper limbs
- Lower limbs

Area Score

Area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by eczema.

Area score Percentage of skin affected by eczema in each region:

- 0 = no eczema in this region
- 1 = 1% – 9%
- 2 = 10% – 29%
- 4 = 30% – 49%
- 4 = 50% – 69%
- 5 = 70% – 89%
- 6 = 90% – 100%: the entire region is affected by eczema

Severity Score

Severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs.

The four signs are:

1. Redness (erythema, inflammation)
2. Thickness (induration, papulation, swelling – acute eczema)
3. Scratching (excoriation)
4. Lichenification (lined skin, prurigo nodules – chronic eczema)

The average intensity of each sign in each body region is assessed as: none (0), mild (1), moderate (2) and severe (3).

Score Intensity of redness, thickness/swelling, scratching, lichenification:

1. 0 = None, absent
2. 1 = Mild
3. 2 = Moderate
4. 3 = Severe

For each region, record the intensity for each of four signs and calculate the severity score.

Severity score = redness intensity + thickness intensity + scratching intensity + lichenification intensity

For each region, multiply the severity score by the area score and by a multiplier.

- Head and neck: severity score × area score × 0.1
- Trunk: severity score × area score × 0.3
- Upper limbs: severity score × area score × 0.2
- Lower limbs: severity score × area score × 0.4

Add up the total scores for each region to determine the final EASI score. The minimum EASI score is 0 and the maximum EASI score is 72.

Appendix E. Patient Report Outcome Scoring

1.0 Worst Pruritus Numerical Rating Scale (NRS)

1.1 Questionnaire

Worst Pruritus Numerical Rating Scale

On a scale 0 to 10, with 0 being "no itch" and 10 being "worst imaginable itch," how would you rate your itch at its worst during the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

No Itch Worst Imaginable Itch

1.2 Scoring Algorithm

The Worst Pruritus NRS will be completed electronically via an onsite tablet device.

1.3 Missing Value Handling

Missing values will not be imputed for the Worst Pruritus NRS.

Appendix F. Activity Schedule

Study Activities Table

Activity *The activities performed at the Week 24 visit of Study M16-046 will be considered the Baseline activity for Study M19-850 (activities with blue checkmarks in Baseline column only).*	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52	Every 12 wks after Wk 52	Unscheduled Visit	PD Visit	30 Days After Last Dose
INTERVIEWS & QUESTIONNAIRES											
Informed consent	✓										
Eligibility criteria	✓										
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk factor questionnaire (annually after last assessment in Study M16-046)					✓			✓ (Wks 80 & 132)			
Review pregnancy avoidance recommendations (females of childbearing potential only)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PROS											
Worst Pruritus NRS	✓	✓	✓	✓	✓	✓	✓		✓	✓	
HN-PGIS	✓	✓		✓							
LOCAL LABS & EXAMS											
Body Weight	✓	✓		✓		✓					

Activity *The activities performed at the Week 24 visit of Study M16-046 will be considered the Baseline activity for Study M19-850 (activities with blue checkmarks in Baseline column only).*	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52	Every 12 wks after Wk 52	Unscheduled Visit	PD Visit	30 Days After Last Dose
Vital Signs (at FU if needed to monitor AEs)	✓	✓		✓		✓		✓			✓
Physical Exam (at follow-up if needed to monitor AEs)	✓										✓
Investigator Assessment (EASI, BSA)	✓	✓	✓	✓	✓	✓	✓		✓	✓	
Chest x-ray (annually after last assessment in Study M16-046 if newly positive TB results)					✓			✓ (Wks 80 & 132)			
12-Lead ECG					✓			✓ (Wks 80 & 132)			
Urine pregnancy test for all female subjects of childbearing age. Monthly home urine pregnancy testing will be performed for visits with > 1 month interval. In case of a positive urine pregnancy test a serum pregnancy test will be performed.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense urine pregnancy tests for monthly home testing			✓	✓	✓	✓	✓	✓			
CENTRAL LABS											
Clinical chemistry, hematology, urinalysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓ (only as needed for AEs)
hsCRP	✓	✓	✓				✓		✓	✓	
QuantiFERON-TB Gold test (and/or local PPD skin test)					✓			✓ (Wks 80 & 132)			

Activity *The activities performed at the Week 24 visit of Study M16-046 will be considered the Baseline activity for Study M19-850 (activities with blue checkmarks in Baseline column only).*	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52	Every 12 wks after Wk 52	Unscheduled Visit	PD Visit	30 Days After Last Dose
Total serum Immunoglobulin E (IgE)	✓	✓		✓			✓				
Optional Biomarker Sample: Skin biopsy (lesional/non-lesional)	✓			✓							
Optional Biomarker Sample: Whole blood (DNA/RNA/Serum/Plasma)	✓	✓		✓			✓				
℞ TREATMENT											
Dispense study drug (excluding Week 52)	✓		✓	✓	✓	✓	✓	✓			