Clinical Study Protocol

AN OPEN-LABEL STUDY OF DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS WHO PARTICIPATED IN PREVIOUS DUPILUMAB CLINICAL TRIALS

Compound:	Dupilumab
Clinical Phase:	3
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Amendment 9 Date of Issue:	12 November 2019
Amendment 8 Date of Issue:	08 Jan 2018 (FI); 04 Jan 2019 (PL)
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Amendment 6 Date of Issue:	28 June 2016
Amendment 5 Date of Issue:	*No date of issue as Amendment 5 was skipped*
Amendment 4 Date of Issue:	26 July 2015
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Scientific/Medical Monitor: [redacted]

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AMENDMENT HISTORY

Amendment 10

Primary Rationale for Amendment 10: The purpose of this amendment is to include a sub-study to assess the safety, pharmacokinetics (PK), and immunogenicity of dupilumab derived from a new manufacturing process in adults with atopic dermatitis (AD). The following table outlines the changes made to the protocol and the rationale.

Change	Rationale	Section Title and Number
Approximately 50 patients who are participating in the current study will be asked to participate in a sub-study using the new dupilumab drug product. Patients who provide informed consent to participate will enter the sub-study at either visit 41, 43, or 44 of the main study and have study treatment switched from current dupilumab drug product to new dupilumab drug product at sub-study visit 1a. Patients will be treated with new dupilumab drug product for at least 12 weeks. Serious or severe injection site reactions (ISRs) or ISRs lasting >24 hours were added as adverse events of special interest (AESIs) for the sub-study. A primary analysis of the sub-study will be conducted after all patients who enter the sub-study complete 12 weeks of treatment with the new dupilumab drug product.	The new sub-study was added to assess the safety, PK, and immunogenicity of dupilumab made from a new manufacturing process (new dupilumab drug product).	Clinical Study Protocol Synopsis: Sub-Study Objectives (new); Study Design; Treatments; Sub-Study Endpoints (new) Section 1.2.3 Rationale for the Sub-Study (new) Section 2.3 Sub-Study Objectives (new) Section 3.1 Study Description and Duration Figure 1 Study Flow Diagram, footnote i (new) Figure 2 Sub-Study Flow Diagram (new) Figure 3 Relationship Between Visit Schedules in Main OLE Study and Sub-Study (new) Section 4.1 Number of Patients Planned Section 4.2.1 Inclusion Criteria Section 4.2.2 Exclusion Criteria Section 4.2.4 Entry Criteria for Sub-Study (new) Section 4.2.4.1 Sub-Study Inclusion Criteria (new) Section 4.2.4.2 Sub-Study Exclusion Criteria (new) Section 5.1 Investigational Treatment Section 6.1 Schedule of Events Table 6 Schedule of Events – Visits 37 (Week 204) through Visits 43 (Week 252), footnote j (new) Table 7 Schedule of Events – End of Treatment, End of Study, Early Termination, Unscheduled Visit, and Re-entry Visit, footnote s (new) Table 8 Sub-Study Schedule of Events (new)

Change	Rationale	Section Title and Number
		Section 6.2.4 Visit 31/Day 1093/Week 156 through Visit 43/Day 1765/Week 252 (+/-3 Days) Section 6.2.5 End of Treatment Visit/Day 1821/Visit 44/Week 260 (+/-3 Days) Section 6.2.6 Sub-Study Treatment Period (new) Section 6.2.6.1 Sub-Study Visit 1a/ Day 1a/Week 0a (±3 days) (new) Section 6.2.6.2 Sub-Study Visit 2a/Day 29a/Week 4a (±3 days) (new) Section 6.2.6.3 Sub-Study Visit 3a/Day 85a/Week 12a (±3 days) (new) Section 6.2.6.4 Sub-Study Visit 4a/Day 169a/Week 24a (±3 days) (new) Section 6.2.6.5 End of Study Visit (Last Dose+12 weeks), Early Termination Visit, and Unscheduled Visits (new) Section 6.2.7 End of Study Visit (84 Days After Last Dose or 12 Weeks After Last Dose) Section 6.2.8 Early Termination Visit Section 6.2.10 Re-entry Visit (Main Study Only) Section 7.2.3 Other Events that Require Accelerated Reporting to Sponsor Section 8.2.3 Sub-Study Endpoints (new) Section 8.3 Pharmacokinetic variable Section 9.5.6 Analysis of the Sub-Study (new) Section 9.5.6.1 Statistical Hypothesis for the Sub-Study (new) Section 9.5.6.2 Justification of the Sub-Study Sample Size (new) Section 9.5.6.3 Analysis Sets for the Sub-Study (new) Section 9.5.6.4 Statistical Methods for the Sub-Study (new)

Change	Rationale	Section Title and Number
The protocol was updated to remove the Kaplan-Meier survival curve from the primary analysis and the secondary endpoint of time to event. The time to event endpoints were used in the first-step analysis to support a regulatory submission. As the first-step analysis has been completed, the time-to-event endpoints and the Kaplan-Meier estimates are no longer needed and have been removed from statistical analysis.	For consistency with the statistical analysis plan (version 2.0).	Clinical Study Protocol Synopsis: Statistical Plan Section 8.2.2 Secondary Endpoints Section 9.5.3 Efficacy Analysis
Language was added to clarify general changes in study conduct in the context of the COVID-19 pandemic. This is in addition to information previously provided directly to sites prior to amendment.	To address guidance from health authorities.	Section 6.1 Study Schedule of Events and Visit Descriptions Section 9 Statistical Plan
Residuals samples will be stored for up to 15 years for exploratory research. Leftover samples may be used to investigate unexpected AEs.	Clarification of storage requirements	Section 6.3.5 Research Testing
Editorial revisions, including update name of the Scientific/Medical Monitor for the study; and update of confidentiality statement on cover page.	For clarity, as needed.	Throughout the protocol

Amendment 9

The purpose of this amendment is to align the dosing regimen of dupilumab with the dosing regimen approved by various regulatory agencies, globally, for this patient population. Criteria for the events that require accelerated reporting to the sponsor were updated to align with current standards for the dupilumab clinical development program. Additionally, the Finland country-specific amendments and Poland country-specific amendments were merged into one global protocol. The following table outlines the changes made to the protocol and the rationale.

Change	Section Changed
The dosing regimen of dupilumab 300 mg was changed from weekly (qw) to every 2 weeks (q2w) starting from visit 25 until the end of the treatment period to match the dosing regimen approved by various regulatory agencies, globally, for this patient population. As dosing of study drug will be less frequent, several in-clinic visits for supplying study drug for at-home administration (V26, 28, 32, 34, 36, 38, 40, and 42) were removed since these visits are no longer needed.	Synopsis: Study Design; Treatments Section 1.2.1 Rationale for Study Design Section 1.2.2 Rationale for Dose Selection Section 3.1 Study Description and Duration Figure 1: Study Flow Diagram; footnote b; footnote h (added) Section 5.1 Investigational Treatment Table 1: Schedule of Events – Visits 1 through 8 (Week 12); footnotes c and l; footnote m (added) Table 2: Schedule of Events – Visits 9 (Week 16) through 18 (Week 52); footnotes a and h; footnote j (added) Table 3: Schedule of Events – Visit 19 (Week 60) through 24 (Week 100); footnotes a and h Table 4: Schedule of Events – Visits 25 (Week 108) through Visit 30 (Week 148); footnotes a and g; footnote i (added) Table 5: Schedule of Events – Visits 31 (Week 156) through Visit 36 (Week 196); footnotes a and g; footnote i (added) Table 6: Schedule of Events – Visits 37 (Week 204) through Visit 43 (Week 252); footnotes a and g; footnote i (added) Table 7: Schedule of Events – End of Treatment, End of Study, Early Termination and Unscheduled Visit; footnotes a and g Section 6.2.2.25 Visit 26/Day 813/Week 116 (+/-3 Days) Section 6.2.2.27 Visit 28/Day 925/Week 132 (+/-3 Days) Section 9.5.2.3 Treatment Exposure

Change	Section Changed
Clarified/updated list of adverse events of special interest (AESIs) including addition of clinically symptomatic eosinophilia and removal of malignancy and suicide-related events per health authority request. The AESI definition for conjunctivitis and blepharitis was revised to remove the criteria for events lasting ≥4 weeks. This change was made because in previous dupilumab trials for the treatment of atopic dermatitis, events of mild to moderate severity were not found to be clinically meaningful, even when lasting >28 days during the study, as they did not result in sequelae or treatment discontinuation. This will enable better characterization of a known adverse event with dupilumab and it also complies with a health authority request.	Section 7.2.3 Other Events that Require Accelerated Reporting to Sponsor
The requirement for reporting pregnancy of a female partner of a male patient during the study or within 12 weeks of the last study drug dose was removed. This requirement was removed from all guidance to investigators in the most current version of the Investigator's Brochure as there has been no evidence of adverse changes to spermatogenesis.	Section 7.2.3 Other Events that Require Accelerated Reporting to Sponsor
Changes outlined in previously issued country-specific amendments for Finland and Poland have been merged.	Section 3.1 Study Description and Duration (includes text that was previously in the PL-specific protocol but not the FI-specific protocol) Section 4.2.3 Entry Criteria for Patients Re-Entering the Study (this section was previously in the PL-specific protocol but not the FI-specific protocol) Section 5.1 Investigational Treatment (includes text that was previously in the PL-specific protocol but not the FI-specific protocol) Table 7: Schedule of Events – End of Treatment, End of Study, Early Termination, Unscheduled Visit and Re-entry Visit (table title, column for re-entry visit, rows, and footnotes pertaining to the re-entry visit were previously in the PL-specific protocol but not the FI-specific protocol) Section 6.2.10 Re-entry Visit (this section was previously in the PL-specific protocol but not the FI-specific protocol)
Minor changes were made to improve clarity, accuracy, and readability.	Throughout the protocol.

Amendment 8 (Poland)

The table that follows outlines the changes made to the protocol and the affected sections:

Change	Section Changed
The purpose of this amendment is to extend the duration of the treatment period to up to 5 years in order to collect longer term safety data. This amendment is notification that as of the date of issue of amendment 8, this study is closed to further enrollment.	Synopsis: Study Design and Study Duration Section 3.1: Study Description and Duration Figure 1: Study Flow Diagram Section 3.2: End of Study Definition (added) Section 4.2.3: Entry Criteria for Patients Re-Entering the Study Section 5.1: Investigational Treatment Table 3: Schedule of Events – Visit 19 (Week 60) through 24 (Week 100) Table 4: Schedule of Events – Visits 25 (Week 108) through Visit 30 (Week 148) Table 5: Schedule of Events – Visits 31 (Week 156) through Visit 36 (Week 196) Table 6: Schedule of Events – Visits 37 (Week 204) through Visit 43 (Week 252) Table 7: Schedule of Events – End of Treatment, End of Study, Early Termination and Unscheduled Visit Section 6.2.4: Visit 31/Day 1093/Week 156 through Visit 43/Day 1765/Week 252 (+/-3 Days) Section 6.2.5: End of Treatment Visit/Day 1821/Visit 44/Week 26 (+/-3 Days) Section 6.2.8: Unscheduled Visits Section 6.2.9: Re-entry Visit

Amendment 8 (Finland)

The table that follows outlines the changes made to the protocol and the affected sections:

Change	Section Changed
The purpose of this amendment is to extend the duration of the treatment period to up to 5 years in order to collect longer term safety data. This amendment is notification that as of the date of issue of amendment 8, this study is closed to further enrollment.	Synopsis: Study Design and Study Duration Section 3.1 Study Description and Duration Figure 1 Study Flow Diagram Section 3.2 End of Study Definition (added) Table 3 Schedule of Events – Visit 19 (Week 60) through 24 (Week 100) Table 4 Schedule of Events – Visits 25 (Week 108) through Visit 30 (Week 148) Table 5 Schedule of Events – Visits 31 (Week 156) through Visit 36 (Week 196) (added) Table 6 Schedule of Events – Visits 37 (Week 204) through Visit 43 (Week 252) (added) Table 7 Schedule of Events – End of Treatment, End of Study, Early Termination and Unscheduled Visit (added) Section 6.2.3 Visit 30/Day 1037/Week 148 (+/-3 Days) (added) Section 6.2.4 Visit 31/Day 1093/Week 156 through Visit 43/Day1765/Week 252 (added) Section 6.2.5 End of Treatment Visit/Day 1821/Visit 44/week 260 (section updated) Section 6.2.6 End of Study Visit (84 Days After Last Dose or 12 Weeks After Last Dose) (section updated) Section 6.2.8 Unscheduled Visits

Amendment 7 (Poland)

The table that follows outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Allow patients who are expected to complete 3 years of treatment prior to regulatory approval to continue treatment through approximately 31 December 2017. Patients who have already completed the End of Treatment visit will be permitted to resume treatment with study drug. Patients who have already completed the End of Study visit will be permitted to re-enter the study. The treatment period will end for all patients on or about 31 December 2017. Add entry criteria for patients who re-enter the study	Synopsis: Study Design and Study Duration Section 3.1: Study Description and Duration Figure 1: Study Flow Diagram Section 4.2.3: Entry Criteria for Patients Re-Entering the Study (section added) Section 5.1: Investigational Treatment Table 4: Schedule of Events – Visits 25 (Week 108) through End of Study (Last Dose + 12 Weeks/84 Days) Section 6.2.3: Visit 30/Day 1037/Week 148 (+/- 3 Days) Section 6.2.4: Visit 31 through Visit 33 (section added) Section 6.2.5: End of Treatment Visit Section 6.2.6: End of Study Visit (84 Days after Last Dose or 12 Weeks after Last Dose) Section 6.2.9: Re-entry Visit (section added)
Update the list of adverse events of special interest (AESIs). Dupilumab has now been studied in more than 4000 patients, with more than 2000 patients exposed for more than 52 weeks. Dupilumab has been approved by the U.S. Food and Drug Administration for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD). There is no evidence of an immunosuppressant effect of dupilumab and no increased risk of serious, severe, or opportunistic infections. Nor is there any evidence of an increased risk of cutaneous T-cell lymphoma. Nearly all injection site reactions (ISRs) are of mild or moderate severity without causing treatment discontinuation and do not warrant increased surveillance. Conjunctivitis will continue to be reported as an adverse event (AE), but only serious, severe, and/or prolonged events of conjunctivitis will require reporting as AESIs. Systemic or extensive hypersensitivity reactions, malignancy (except basal cell carcinoma), and serious, severe, and/or prolonged events of blepharitis and keratitis have been added as AESIs.	Section 7.2.3: Other Events that Require Accelerated Reporting to Sponsor

Change	Section Changed
Modify the criteria for which study drug may be temporarily discontinued	Section 5.2.2.2: Reasons for Temporary Discontinuation of Study Drug
Remove "treatment with systemic corticosteroids" as a reason for temporary discontinuation of study drug and from the List of Prohibited and Restricted Medications. Patients are no longer required to temporarily discontinue study drug if they are also treated concomitantly with systemic corticosteroids. As there is no evidence that dupilumab is an immunosuppressant, the theoretical basis for avoiding combined treatment with dupilumab and systemic corticosteroids is no longer valid.	Section 5.2.2.2: Reasons for Temporary Discontinuation of Study Drug Section 5.5.1: Permitted Medications and Procedures Section 5.5.2: Prohibited and Restricted Medications
Reduce the duration of the End of Study visit from 16 weeks to 12 weeks after the last dose of dupilumab. Pharmacokinetic (PK) analysis of the once every week (qw) dosing regimen demonstrates that the median time to non-detectable concentrations after the last steady-state dose is approximately 12 weeks.	Synopsis: Study Design Section 3.1: Study Description and Duration Figure 1: Study Flow Diagram Section 4.2.2: Exclusion Criteria, exclusion criterion 23 Table 4: Schedule of Events – Visits 25 (Week 108) through End of Study (Week 160) Section 6.2.6: End of Study Visit/ Visit 31/Day 1121 (or 84 Days after Last Dose)/Week 160 (or 12 Weeks after Last Dose) Section 6.2.7: Early Termination Visit Section 7.2.3: Other Events that Require Accelerated Reporting to Sponsor
Update the sample size since no new patients are expected to be enrolled in this trial	Synopsis: Sample Size Section 4.1: Number of Patients Planned

Amendment 7 (Finland)

The table that follows outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Update the list of adverse events of special interest (AESIs). Dupilumab has now been studied in more than 4000 patients, with more than 2000 patients exposed for more than 52 weeks. Dupilumab has been approved by the U.S. Food and Drug Administration for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD). There is no evidence of an immunosuppressant effect of dupilumab and no increased risk of serious, severe, or opportunistic infections. Nor is there any evidence of an increased risk of cutaneous T-cell lymphoma. Nearly all injection site reactions (ISRs) are of mild or moderate severity without causing treatment discontinuation and do not warrant increased surveillance. Conjunctivitis will continue to be reported as an adverse event (AE), but only serious, severe, and/or prolonged events of conjunctivitis will require reporting as AESIs. Systemic or extensive hypersensitivity reactions, malignancy (except basal cell carcinoma), and serious, severe, and/or prolonged events of blepharitis and keratitis have been added as AESIs.	Section 7.2.3 : Other Events that Require Accelerated Reporting to Sponsor
Modify the criteria for which study drug may be temporarily discontinued	Section 5.2.2.2 :Reasons for Temporary Discontinuation of Study Drug
Remove “treatment with systemic corticosteroids” as a reason for temporary discontinuation of study drug and from the List of Prohibited and Restricted Medications. Patients are no longer required to temporarily discontinue study drug if they are also treated concomitantly with systemic corticosteroids. As there is no evidence that dupilumab is an immunosuppressant, the theoretical basis for avoiding combined treatment with dupilumab and systemic corticosteroids is no longer valid.	Section 5.2.2.2 : Reasons for Temporary Discontinuation of Study Drug Section 5.5.1 :Permitted Medications and Procedures Section 5.5.2 : Prohibited and Restricted Medications

Change	Section Changed
Reduce the duration of the end-of-study visit from 16 weeks to 12 weeks after the last dose of dupilumab. Pharmacokinetic (PK) analysis of the once every week (qw) dosing regimen demonstrates that the median time to non-detectable concentrations after the last steady-state dose is approximately 12 weeks.	Synopsis: Study Design Section 3.1 : Study Description and Duration Figure 1 :Study Flow Diagram Section 4.2.2: Exclusion Criteria, exclusion criterion 23 Table 4 : Schedule of Events – Visits 25 (Week 108) through End of Study (Week 160) Section 6.2.3 : End of Study Visit/Visit 31/Day 1121 (or 84 Days after Last Dose)/Week 160 (or 12 Weeks after Last Dose) Section 6.2.5 : Early Termination Visit Section 7.2.3 : Other Events that Require Accelerated Reporting to Sponsor
Update the sample size since no new patients are expected to be enrolled in this trial	Synopsis: Sample Size Section 4.1 : Number of Patients Planned

Amendment 6 (28 June 2016)

The main purpose of this amendment is to streamline and simplify the schedule of study visits and procedures. This is expected to facilitate the implementation of the protocol at participating study centers, decrease the burden for study patients, and improve their compliance. At the time of implementing this amendment, data has been generated from more than 1400 patients who have followed a more intensive schedule of visits and assessments. More than 400 patients have completed one year in the study. Consequently, at this stage, it has become possible to remove the non-essential visits and assessments.

Specific changes in this amendment include:

- To align the Global, Great Britain (GB), and Japan (JP) protocol amendment numbers for ease of operation
- Update rationale for dose selection to indicate that the dose ranging study R668-AD-1021 is now complete and to provide rationale for 300 mg QW dose
- Update study description to justify abbreviation of visits in this amendment
- Remove the following visits at the following weeks from the Schedule of Events and throughout the protocol: week 1, week 2, week 3, week 8, week 20, week 28, week 36, and week 44. This was deemed acceptable from a patient safety standpoint based on data from completed phase 3 studies
- Remove the genomic sub-study DNA sample (optional) from the Schedule of Events and throughout the protocol
- Remove the informed consent form (ICF) for optional assessments from the Schedule of Events as it is no longer needed because the optional sample for DNA analysis has also been removed

- Remove the concomitant medications/procedures assessment from visits at week 12, week 24, week 40, week 52, week 68, week 84, week 100, week 116, week 132, and week 148
- Remove the Patient Oriented Eczema Measure (POEM), Dermatology Quality of Life Index (DLQI), and EQ-5D assessments from visits at screening, week 12, week 24, week 76, week 124, End of Treatment, End of Study, Early Termination, and Unscheduled visit to simplify study conduct
- Remove patient global assessment of disease from the Schedule of Events and throughout the protocol. This was deemed appropriate from a patient safety standpoint based on data from completed studies.
- Remove patient global assessment of treatment effect from the Schedule of Events and throughout the protocol. This was deemed appropriate from a patient safety standpoint based on data from completed studies.
- Remove research samples (serum/plasma) from the Schedule of Events and throughout the protocol. It is non-essential and this was deemed appropriate from a safety standpoint based on data from completed studies.
- Remove electrocardiogram from the Schedule of Events and throughout the protocol. This was deemed appropriate from a patient safety standpoint based on data from completed studies.
- Remove urinalysis from the Schedule of Events and throughout the protocol. This was deemed appropriate from a patient safety standpoint based on data from completed studies.
- Remove the thymus and activation-regulated chemokine (CCL17 [TARC]) assessment from the Schedule of Events and throughout the protocol.
- Remove the total serum IgE assessment from the Schedule of Events and throughout the protocol.
- Remove high-sensitivity C-reactive protein (hs-CRP), anti-nuclear antibody (ANA), anti-dsDNA, and anti-thyroid peroxidase antibody (anti-TPO) assessments from the Schedule of Events and throughout the protocol.
- Remove all physical exams except for at baseline. This was deemed appropriate from a patient safety standpoint based on data from completed studies.
- Remove hematology and chemistry from all visits except visit 1 (screening), visit 2 (baseline), week 16, week 48, week 100, week 148, and unscheduled visits
- Remove Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) from visits at week 12, week 24, 32, week 40, week 68, week 76, week 84, week 92, week 108, week 116, week 132, week 140, and week 148 (End of Treatment visit)
- Remove vital signs assessments from visits at week 12, week 24, week 40, week 52, and week 68

- Remove weight assessment from the visit at week 24
- Remove drug concentration samples from visits at week 4, week 12, week 52, week 60, week 68, and week 116. Add drug concentration samples to week 48 and week 100.
- Update the Schedule of Events to clarify that patients will be provided with a pregnancy test kit to take home for monthly testing in between clinic visits, or may choose to have the testing done at the study site
- Remove anti-drug antibody (ADA) samples from the visits at week 4, week 12, week 52, week 68, week 92, and week 116. Add ADA at week 48, week 100, week 124, and End of Treatment visit
- Addition of an ophthalmological examination to the Schedule of Events at baseline, week 4, week 12, week 16, week 32, week 48, week 60, week 76, week 92, week 108, week 124, week 140, end of study visit, and unscheduled visits
- Remove the 3 day window for the End of Study visit and indicate that a late visit is acceptable and preferable to foregoing the assessments altogether
- Update the number of global study sites and patients planned
- Clarify dosing language
- Clarify how long patients treated with a prohibited or restricted medication must temporarily discontinue from study drug
- Clarify inclusion criterion 1b to allow enrollment of patients who participated in any dupilumab atopic dermatitis (AD) study that has undergone last visit
- Change the wording in exclusion criterion 3 to allow enrollment of patients who met conditions for permanent study drug discontinuation in a prior study if such conditions were considered resolved and of no further consequence – subject to medical monitor review and approval
- Update exclusion criterion 12 to add that patients with positive hepatitis C antibody may undergo additional tests and consultations
- Update exclusion criterion 23 to state that use of effective and accepted contraception applies only when patients engage in heterosexual intercourse and to add double barrier methods as accepted method of contraception
- Remove severe laboratory abnormalities as reason for permanent discontinuation of study drug. This event is now listed as a reason for temporary discontinuation of study drug.
- Clarify that “Pregnancy at any time during the study” is a reason for permanent discontinuation of study drug
- Clarify when elevated creatine phosphokinase (CPK) should be considered a reason for temporary discontinuation of study drug

- Align the text describing severe infection as a reason for temporary discontinuation of study drug with the AESI criteria
- Add suicide-related events and conjunctivitis to AESI
- Remove the section Restricted Concomitant Medications and Procedures to consolidate information under "Prohibited and Restricted Medications"
- Update secondary endpoints to reflect removal of some assessments

Amendment 5

This amendment number was skipped to align the Global, GB, and Japan protocol amendment numbers for ease of operation.

Amendment 4 (26 July 2015)

The purposes of this amendment are to:

- Extend the study duration for each patient to up to 3 years or until the product is commercially available in the geographic region of the patient (whichever comes first) to allow patients to continue treatment with dupilumab in the study prior to product becoming available.
- Update the estimated planned enrollment to approximately 2000 to reflect patients in the phase 3 studies expected to roll over into this study and the number of study sites to approximately 550 globally to reflect the number of study sites in the phase 3 studies expected to participate in this study.
- Revise inclusion criterion 1 to allow enrollment of patients in this open-label study who have been screened for a phase 3 study (R668-AD-1334 and -1416), but could not be randomized in the phase 3 studies due to randomization closure, to provide these patients (who meet the eligibility criteria for this open-label study) the opportunity for dupilumab treatment; and to make edits for clarity
- In exclusion criterion 5, change the washout period for prohibited medications from 1 week to 5 half-lives to be consistent with the parent studies, such as the phase 3 studies.
- Clarify and simplify exclusion criterion 9 regarding infections indicating a patient with any infection requiring systemic treatment that is not resolved within 1 week before baseline will not be eligible to enroll in the study.
- Clarify exclusion criterion 12 to indicate that a given hepatitis virus, antigen, or antibody test is not required for patients with a negative result of that test documented within 1 year prior to baseline, and to clarify serology tests necessary to rule out active hepatitis B infection and carrier status.
- Add ECG at week 100 visit (end of year 2) and change ECG at the end of study visit to end of treatment visit.
- Add additional laboratory tests at the unscheduled visit, and a note that not all listed procedures and tests are required at the visit.

- Change "electrocardiograms will be performed before blood is drawn during visits requiring blood draws" to "electrocardiograms should be performed before blood is drawn during visits requiring blood draws" to allow slight flexibility in this long-term study.
- Add a note in the Other Laboratory Tests section indicating that HIV testing is not required at screening for patients with a negative test result in the parent study within 1 year of baseline to be consistent with exclusion criterion 11; and to add a note to clarify policy and procedure for unplanned laboratory tests.
- Add the following footnote for laboratory tests to be consistent with the phase 3 studies: "direct and indirect bilirubin will be measured when the total bilirubin is above the upper limit of normal (ULN); CPK isoenzymes will be measured when CPK >5X the ULN".
- Remove the requirement to have some patients who are negative for anti-drug (dupilumab) antibody (ADA) at their last study visit to have additional ADA samples collected for analysis (which was intended to maintain blind) because maintaining blind is not necessary in this open-label study, and to revise the criteria for additional ADA follow-up for patients with an positive ADA titer at their last study visit to provide flexibility as the criteria may be adjusted according to new ADA data and knowledge accumulated.
- Specify that research samples may be stored for up to 10 years.
- Remove "by telephone" for pregnancy reporting to allow reporting by other means (eg, filling out and faxing the pregnancy form).
- In the statistical methods for efficacy analysis section, remove censoring of efficacy data during data analysis based on use of prohibited concomitant treatment because it is inappropriate or not practical in this long-term study where study treatment is allowed to resume after certain period following completion of prohibited concomitant medications; and to add a statement that subgroup analyses for key efficacy endpoints will be performed.
- Revise the definition of EASI-75 to be consistent with that in the phase 3 dupilumab protocols.
- Add Pruritus NRS related endpoints to the secondary endpoint section to be consistent with the phase 3 dupilumab protocols.

Amendment 3 (12 January 2015)

The purposes of this amendment are to:

- Update information about study drug formulation to indicate availability of prefilled syringes (PFS) and to remove mention of glass vials.
- Clarify that assessments in the screening visit in this study that coincide with assessments in the last visit in the previous study will be performed only once
- Clarify that it is currently anticipated that approximately 800 patients who participated in controlled and/or short-term dupilumab studies will enroll in this study, but the actual size of the study population will depend on the number of patients transitioning from prior dupilumab studies, so the anticipated number is not proposed as a fixed enrollment goal.
- Add a statement that patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened.
- Add study R668-AD-1021 to the list of completed studies excepted from the specific compliance requirements.
- Clarify that patients who discontinued from the previous dupilumab study due to protocol-defined criteria for permanent discontinuation are not eligible to participate in this study.
- State that patients with active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before day 1 are not eligible to participate in this study.
- Add hepatitis B core antibody (HBcAb) to the list of tests in exclusion #12, that are not required at screening if patients had a negative test result within 1 year prior to baseline.
- Delete history of nonmalignant lymphoproliferative disorders as an exclusion criterion to harmonize with other dupilumab protocols, as this exclusion is implicitly covered under other criteria.
- Delete the redundant statement that if necessary, study staff will train the patient or caregivers who are willing to administer study drug outside of the clinic, on preparation and administration of study drug.
- Add the upper arms as an optional site for administration of study drug.
- Add a note to state that patients who discontinue the study because of a laboratory abnormality may resume study treatment when the laboratory abnormality is sufficiently normalized if a causal relationship to study drug can be reasonably excluded, and that the decision to resume study treatment will be made jointly by the investigator and medical monitor.
- State that a review of efficacy will be triggered whenever patients fail to achieve and/or maintain Eczema Area and Severity Index (EASI)-25 at week 12.

- Remove the redundant statement that treatment with any prohibited concomitant medication or procedure may lead to temporary discontinuation from the study.
- Delete the statement that study drug dosing could be temporarily discontinued in the event of confirmed alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3 x upper limit of normal (ULN), total bilirubin >2 x ULN excluding confirmed Gilbert's Syndrome, or confirmed AST and/or ALT >5 x ULN (for more than 2 weeks) from Section 5.2.2.2, as these criteria are noted in Section 5.2.2.1 as reasons for permanent discontinuation.
- Add treatment with systemic corticosteroids or nonsteroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors, biologic agents) as a reason for temporary discontinuation of study drug.
- Delete phototherapy as a reason for temporary discontinuation of study drug.
- Clarify that study drug dosing may resume at the discretion of the principal investigator in consultation with the medical monitor after the laboratory abnormality leading to suspension of dosing normalizes sufficiently, and/or the medication leading to suspension of dosing has been discontinued.
- Confirm that the investigator may discontinue study drug dosing at any time if necessary to ensure the safety of study patients.
- Add basic skin care, emollients, topical anesthetics, antihistamines, topical and systemic anti-infective medications, topical calcineurin inhibitors, and topical corticosteroids to the list of permitted medications.
- Add systemic corticosteroids and nonsteroidal systemic medications as prohibited medications.
- Delete nonsteroidal systemic immunomodulating medications as prohibited medications.
- Clarify that patients who receive prohibited medications will be discontinued from study drug for the duration of treatment with these prohibited medications plus 5 half-lives.
- Add HIV screening, and hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C antibody assessments at screening.
- Specify the preferred order of assessments prior to injection of study drug.
- Clarify the purpose of collection of research samples.
- Add that a pregnancy occurring in a female partner of a male patient participating in the study during the study or within 16 weeks of the last dose of study drug must be reported by the investigator to the sponsor (or designee) by telephone within 24 hours of identification.
- Add mycosis fungoides and other forms of cutaneous T cell lymphoma as an adverse event of special interest (AESI).

Amendment 2 (12 June 2014)

The purposes of this amendment are:

- To change the weekly dose of dupilumab from 200 mg to 300 mg and the loading dose from 400 mg to 600 mg based on the interim results from the dose ranging study (R668-AD-1021).
- To revise inclusion criterion #1, removing the requirement of 4-week study treatment in a parent study to allow more patients to become eligible, especially those who may have discontinued the parent study sooner than 4 weeks of treatment due to being on placebo; clarifying visits/assessments required to be completed in the parent study for a patient to be eligible to participate in this study to prevent accelerated entry into this study.
- To add an inclusion criterion to clarify that only adult patients (≥18 years of age) are eligible to participate in this study.
- To revise exclusion criteria #1, 2, and 3 for clarity and consistency.
- To revise exclusion criterion #5, reducing washout period for the listed prior medications from 4 weeks to 1 week.
- To revise exclusion criteria #9, 10, and 11 for clarity or accuracy.
- To remove hepatitis B core antibody (HBcAb) from exclusion criterion #12 and schedule of assessments.
- To change the requirement for adequate birth control from up to 16 weeks to up to 120 days after the last dose of study drug in exclusion criterion #24.
- To revise Section 5.2.2.1 Reasons for Permanent Discontinuation of Study Drug and Section 5.2.2.2 Reasons for Temporary Discontinuation of Study Drug for clarity and to be consistent with other dupilumab clinical studies where appropriate.
- To remove ultraviolet procedures from the list of restricted concomitant medications and procedures.
- To change the 1-hour postdose close monitoring to be a minimum of 30 minutes at visits 2 to 4, and to remove the 1-hour postdose close monitoring from visits 5 and 6.
- To add Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly) at the end of study visit.
- To specify that the pregnancy test will be performed with urine sample at visits 2, 6 to 23, as well as at the end of treatment, end of study, early termination, and unscheduled visits.
- To correct that the Investigator's Global Assessment (IGA) is a 5-point scale (instead of 6-point).
- To correct that the Pruritus Numerical Rating Scale will be completed weekly (instead of daily).

- To revise the description of anti-drug (dupilumab) antibody (ADA) measurements and samples to be clear on how patients with an ADA titer ≥240 at the last study visit will be monitored.
- To add the following statement "Unused samples collected for drug concentration or ADA analyses may also be used for research purposes".
- To change the secondary endpoint of "proportion of patients with EASI-50" to "proportion of patients with EASI-75" to be consistent with phase 3 studies and to clarify that the change in EASI is in reference to baseline of the parent study.
- To clarify the observation periods for analyses of safety variables.
- To clarify that summarization of potentially clinically significant values (PCSVs) for laboratory results will be performed for treatment-emergent PCSVs.
- To revise the calculation of duration of exposure during the study from "(date of last study drug injection – date of first study drug injection) + 14 days" to "(date of last study drug injection – date of first study drug injection) + 7 days".

Amendment 1 (12 December 2013)

Purpose:

The purposes of this amendment are:

- To add the monitoring of efficacy associated with long-term treatment to the secondary objective of the study, as efficacy procedures are performed in this study.
- To add the use of "systemic corticosteroids" and "systemic immunosuppressive drugs" to the list of other secondary endpoints, to allow for more specific analyses.
- To specify the requirements for patients to assess the overall (average) intensity of their pruritus using a 10-point numerical rating scale (NRS) on a weekly basis, which was inadvertently omitted in the original version of the protocol.
- To move the IVRS/IRWS training from screening to baseline, and to add a second IVRS/IWRS training time point at week 4 (visit 6), to be proximate to the time at which the patient is eligible to take drug home for self-injection; the IVRS/IWRS will be used to capture dosing diary information when patients dose from home.
- To change the dosing window for visits with windows of "± 4" and "± 7 days" to "± 3 days." Visit windows have been defined as "± 3 days" to avoid overlapping windows for weekly dosing.
- To add measurement of "height" to the list of procedures and assessments performed in the study (inadvertently omitted in the original version).

- To clarify that in order to become eligible for the open-label extension study, patients enrolled in previous AD studies must adequately complete the assessments required for both the treatment and follow-up periods of those particular studies; to further clarify that adequate completion of these assessments includes undergoing at least 2 landmark visits, as defined in each study protocol: (1) primary endpoint visit, which is usually the end of treatment visit, and (2) end of study visit as defined in each study protocol, as well as completing all other assessments during the treatment and follow-up periods for at least 50% of the timepoints allocated to each assessment, unless the protocol of the previous study allows earlier transition into the open-label extension, in which case these requirements apply up to the point when this transition is permitted.
- To remove systemic corticosteroids (including topical and oral) as a prohibited and restricted medication. Since this is a long-term study, it is anticipated that some patients may use systemic corticosteroids for the treatment of concurrent atopic conditions, such as asthma, which are commonly associated with AD.
- To clarify that resumption of study treatment after temporary discontinuation will require written approval from the medical monitor.
- To add inadequate efficacy as a reason for permanent discontinuation from the study drug, and from the study in response to the German Ethics Committee request.
- To remove the requirement to administer 400 mg SC dupilumab as a loading dose (ie, 200 mg initial dose, and 200 mg loading dose) for patients treated in a previous AD study unless the last dose administered is less than 4 weeks before their first dose in the current study. These patients will only receive 200 mg as their first dose in the current study, as their dupilumab plasma concentration may be high as a result of their participation in their previous study.
- To clarify that training on self- injection or injection administered by a caregiver will not be required if training occurred in the previous study; to remove the requirement that patients will be monitored at the study site for 1 hour after each of the first 5 injections.
- To remove inclusion criterion #2 requiring IGA ≥2 at baseline in the current study to account for patients who may transition into the study directly from the dosing phase in the previous study. Many of these patients may have low disease severity scores.
- To more clearly define the basis on which a patient will be excluded from the open-label extension study.
- To modify exclusion criterion #6 prohibiting treatment with biologics other than dupilumab in the past 12 months for any indication, or 5 years for dermatological indications, to the new requirement of within 5 half-lives (if known), or 16 weeks, whichever is longer, before the first dose in the open-label extension study. Because patients were already screened for this exclusion criteria in their previous studies, this criteria was modified so as not to screen out patients who participated in clinical trials with biologics for AD (eg, Stelara) in the past 5 years.

- To clarify that any history of HIV and/or hepatitis seropositivity, if known at the time of the screening visit, will render the patient ineligible for the study, and to remove all requirements for human immunodeficiency virus (HIV) and hepatitis B testing at screening. This change was made because patients in this study already underwent similar screening in their previous study.
- To clarify that the screening visit in this study may coincide with the last visit in the previous study. Assessments that are common to both studies will be performed only once.
- To remove the HbA1C testing requirement from the study, which was erroneously included among the laboratory tests to be performed.
- To add the performance of a physical examination to the end of treatment visit.
- To permanently discontinue from the study patients who received prohibited medications. These patients will be asked to complete the assessments of the early termination and end of study visits, as described in the protocol.
- To remove the requirement that efficacy measurements be collected prior to administering prohibited medications or procedures which are not critical in an open-label safety study.
- To clarify that patients will document/report compliance in a patient dosing diary via IVRS/IWRS.
- During year 1, to change the requirement for performance of a urine pregnancy test in the clinic from every 12 weeks to every month. During year 2, to distribute pregnancy test kits at clinic visits for monthly pregnancy testing in between clinic visits.
- To allow a local physician, qualified by training and experience, to review ECGs, to accommodate those sites that do not have access to a cardiologist.
- To require SAEs be entered into the EDC within 24 hours.
- To remove the pregnancy reporting requirement for a female partner of a male patient, and the requirement to follow-up on the pregnancy of a female partner of a male patient enrolled in the study.
- To remove the key secondary endpoint of "number of disease-free days per patient year" from the protocol. As assessments are not conducted on a daily basis, these cannot be assessed.
- To add language regarding the impact of dupilumab on cytochrome P450 (CYP) enzyme activity.
- To correct typographical errors, clarifications to wording of key secondary endpoints, statistical plan, rational for study design and dose selection, several inclusion/exclusion criteria, clarification of definition of on-treatment, and post-treatment period for the analysis of TEAEs, clarification of time period for calculation of treatment exposure, and to reorder the presentation of safety and efficacy. As this is a safety study, safety is presented first.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	AN OPEN-LABEL STUDY OF DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS WHO PARTICIPATED IN PREVIOUS DUPILUMAB CLINICAL TRIALS
Site Locations **Principal Investigator**	Approximately 500 global study sites.
Objectives	The primary objective is to assess the long-term safety of dupilumab administered in adult patients with atopic dermatitis (AD). The secondary objective of the study is to assess the immunogenicity of dupilumab in adult patients with AD, in the context of re-treatment, and to monitor efficacy parameters associated with long-term treatment.
Sub-Study Objectives:	The primary objective of the sub-study is to assess the safety of the new dupilumab drug product in adult patients with AD after switching from current dupilumab drug product. The secondary objectives of the sub-study are to evaluate systemic exposure and immunogenicity of the new dupilumab drug product in patients with AD.
Study Design	This is a multicenter, open-label extension (OLE) study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD who have previously participated in controlled studies of dupilumab or have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized due to randomization closure. Enrollment will take place at approximately 500 global study sites. After providing informed consent, patients will be assessed for study eligibility at the screening visit. The screening visit in this study may coincide with the last visit in the previous study, in which case assessments that are common to both studies will be performed only once. A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg SC dupilumab weekly (qw) starting on day 8. For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg qw to every 2 weeks (q2w). Patients will return for visits that are spaced 4 to 16 weeks apart, as specified in the protocol. The study treatment duration will be up to 5 years. The end of study visit occurs 12 weeks after the end of treatment visit. As of the date of issue of amendment 8, this study is closed to further enrollment.

	Approximately 50 patients who are participating in the current ongoing OLE study (R668-AD-1225) and have not completed the end of treatment visit (ie, visit 44) prior to the implementation of amendment 10 will be asked to participate in the sub-study. After providing informed consent, eligible patients who agree to participate will enter the sub-study at either visit 41, 43, or 44 of the main study and have study treatment switched from the current dupilumab drug product to the new dupilumab drug product at sub-study visit 1a. Dupilumab dosing will remain 300 mg SC q2w, and patients will be treated with the new dupilumab drug product 300 mg SC q2w for at least 12 weeks (some patients may be treated for 24 weeks). The end of study visit for patients participating in the sub-study under amendment 10 will be 84 days (12 weeks) after the last dose using the new dupilumab drug product. Patients who enter the sub-study from either visit 43 or visit 44 of the main study will have the duration of their study treatment increased by 4 or 12 weeks, respectively. Patients and/or caregivers who are willing and able to administer dupilumab doses outside the clinic will be trained on injecting study drug unless they had already been trained during their participation in the previous study. These patients will self-inject study drug (or have the drug administered by a caregiver) during weeks in which no clinic visit is scheduled. Safety, laboratory, and clinical assessments will be performed at specified clinic visits. Patients who receive treatment with a prohibited or restricted medication will be discontinued from study drug for the duration of the prohibited treatment (plus 5 half-lives as applicable). Study treatment may be resumed only if approved by the medical monitor. Patients who test positive for anti-drug antibody (ADA) at their last study visit (early termination or end of study) may, based on the benchmark ADA titer in effect at the time, be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months until their titers fall below the benchmark titer.
Study Duration	The study treatment duration will be up to 5 years.
Population	
Sample Size:	The study is open to patients who participated in controlled and/or short-term dupilumab clinical trials or have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized because of randomization closure. Based on the numbers of patients enrolled or screened in the antecedent dupilumab studies, it is currently anticipated that approximately 2500 patients will be enrolled. Institutional Review Boards (IRBs)/Ethics Committees (ECs) will be notified if there is more than 25% greater participation than currently anticipated.
Target Population:	The target population includes adult (≥18 years of age) patients with AD who participated in a prior dupilumab clinical study.

Treatments	
Study Drug	Dupilumab
Dose/Route/Schedule	300 mg SC qw for patients who complete the study prior to the implementation of amendment 9 300 mg SC q2w after implementation of amendment 9 For the sub-study: new dupilumab drug product 300 mg SC q2w (after implementation of amendment 10) A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study.
Endpoints	
Primary:	The primary endpoint in the study is the incidence and rate (events per patient-year) of treatment-emergent adverse events (TEAEs) through the last study visit.
Secondary:	The key secondary endpoints are: • Incidence and rate (events per patient-year) of serious adverse events (SAEs) and adverse events (AEs) of special interest (AESIs) • Proportion of patients with Investigator's Global Assessment (IGA) = 0-1 at each visit • Proportion of patients with Eczema Area and Severity Index (EASI) -75 (≥75% reduction from baseline in EASI scores) at each visit
Sub-Study Endpoints	
Primary:	The primary endpoint in the sub-study is the incidence of AESIs through the last study visit after switching to the new dupilumab drug product.
Secondary:	Secondary endpoints of the sub-study are: • Trough concentrations of functional dupilumab in serum before and after switching to the new dupilumab drug product • Incidence of treatment-emergent ADA response in patients receiving the new dupilumab drug product
Procedures and Assessments	The safety of dupilumab in this population will be assessed by evaluating TEAEs, detailed medical history, vital signs, and clinical laboratory testing. Concomitant medications and procedures will be collected at time points specified in the protocol. Blood samples will be collected for drug concentration and ADA levels at predetermined time points. The efficacy of dupilumab in this population will be assessed by AD disease severity scores and quality of life (QOL) questionnaires.

Statistical Plan	The safety analysis set (SAF) will include all patients who received any study drug; it is based on the treatment received (as treated). Efficacy, treatment compliance/administration, and all clinical safety variables will be analyzed using the SAF, as treated. Descriptive statistics of the efficacy endpoints will be summarized for this open-label study. These include the proportions for category endpoints and basic statistics of original, absolute, and percentage change from baseline for continuous endpoints. All observed data will be used for analysis. A summary of safety results (reported TEAEs and clinical laboratory evaluations) will be presented. The following drug concentration analyses will be conducted: descriptive statistics at each sampling time and least square mean analysis for concentration at steady-state. No formal statistical analysis will be performed. Listings of ADA positivity and titers presented by patient and time point will be provided. Prevalence of ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by titer level.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Definition of Terms
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ARISg	A pharmacovigilance and clinical safety software system
AST	Aspartate aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Paper or electronic case report form
CRO	Contract research organization
C_{trough}	Trough concentration
$C_{trough,ss}$	Trough concentration at steady state
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E

Abbreviations	Definition of Terms
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional review board
ISR	Injection site reaction
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
OLE	Open-label extension
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PFS	Prefilled syringe
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PT	Preferred term
q2w	Once every 2 weeks
q4w	Once every 4 weeks
QOL	Quality of life
qw	Once every week
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SOC	System organ class
SOE	Schedule of events
TEAE	Treatment-emergent adverse event
Th1	Type 1 helper T cell
Th2	Type 2 helper T cell
TNF	Tumor necrosis factor
TPO	Anti-thyroid peroxidase antibody

Abbreviations	Definition of Terms
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (eg, itchiness), and by scaly and dry eczematous lesions. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to major psychological problems, significant sleep loss, and impaired quality of life (QOL) that leads to high socioeconomic costs. An estimated 15% to 30% of children and 2% to 10% of adults are affected by AD (Beiber 2008).

The pathophysiology of AD is influenced by a complex interplay between immunoglobulin E (IgE)-mediated sensitization, the immune system, and environmental factors. The primary skin defect may be an immunologic disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that could be the consequence of both genetic mutations and local inflammation.

Skin-infiltrating lymphocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the patho-physiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes, including Langerhans cells and inflammatory dendritic epithelial cells, polarize T-helper cells via IgE- and non-IgE-mediated mechanisms. Dendritic cells in the skin take up and present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, chemokine 'C' receptor (CCR4+) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5; whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine, thymic stromal lymphopoietin, in AD lesions which may amplify and sustain the allergic response.

Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha (IL-4Rα) subunit, which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor system. The binding of dupilumab to IL-4Rα results in blockade of the function of both IL-4 and IL-13 signal transduction. Dupilumab is under development as a potential novel treatment for AD and asthma.

The goal in treating AD is reducing skin inflammation and controlling the symptoms. Therapy has been focused on trying to control the T helper cell response. Topical corticosteroids are overwhelmingly the most frequently prescribed class of drugs; however, long term application of topical corticosteroids is not recommended because of the risk of skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, growth retardation, hypothalamic-pituitary axis effects, etc.). Topical calcineurin inhibitors are generally effective and safe as short-term treatments, but concerns of skin malignancies and increased risk of lymphomas have prompted regulatory authorities to require a warning in the prescribing information of topical tacrolimus and pimecrolimus. Repeated application of any topical therapy over a long period of time leads to reduced patient compliance. Antihistamines, which are

primarily sedating, are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited. Oral immunosuppressants (Schmitt 2007) and glucocorticoids are effective, but are sometimes associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy. Patients' disease often rebounds when the treatment is stopped, especially after the administration of systemic glucocorticoids (Schmitt 2009, Schram 2012, Akhavan 2008). Biological agents including anti-tumor necrosis factor (TNF) α, anti-IgE (omalizumab), anti-IL-5 (mepolizumab), and anti-CD11a (efalizumab) have generally been ineffective in clinical trials.

Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab targets the IL-4Rα and thus interferes with the signaling cascade. Inhibition of this Th2 inflammatory pathway is currently or has previously been evaluated with other agents.

Dupilumab is being developed as a potentially safer alternative to oral corticosteroids, calcineurin inhibitors, and other systemic immunosuppressive drugs such as methotrexate, cyclosporine, and azathioprine, which have numerous and considerable side effects including diabetes, hypertension, and osteoporosis for corticosteroids (as well as the risk of rebound after steroid discontinuation), myelosuppression and hepatotoxicity for methotrexate, nephrotoxicity and hypertension for cyclosporine, and gastrointestinal disturbances and leucopenia for azathioprine. In addition, the broad immunosuppression caused by these drugs carries an increased risk of developing serious bacterial, fungal, viral, and mycobacterial infections, compared with the targeted Th2 inhibition.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Rationale

1.2.1. Rationale for Study Design

The primary purpose of the study is to collect long-term safety data on patients treated with dupilumab to better understand the safety profile and help fulfill the anticipated safety database requirements for long-term exposure.

This study may be an incentive to patients enrolling in placebo-controlled trials (eg, phase 2b and phase 3), as patients are eventually provided with the opportunity to receive dupilumab treatment in this study even if previously randomized to placebo.

Eligible patients must have received any study treatment and completed the specified assessments in the prior dupilumab controlled study or have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized because of randomization closure. This study will provide useful information on re-exposure to dupilumab, particularly regarding the potential for immunogenicity associated with a new course of treatment, as well as the relationships between anti-dupilumab antibodies, dupilumab serum (trough) concentration, and clinical parameters.

1.2.2. Rationale for Dose Selection

Patients enrolled in this study initially received weekly (qw) doses of 300 mg subcutaneous (SC) dupilumab.

A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8.

A phase 2b dose-ranging study (R668-AD-1021) evaluated dupilumab dose regimens of 300 mg qw, 300 mg once every 2 weeks (q2w), 300 mg q4w, 200 mg q2w, and 100 mg q4w versus placebo administered for 16 weeks. This study indicated that dupilumab 100 mg q4w had suboptimal efficacy, whereas the 300 mg qw dupilumab regimen demonstrated the highest efficacy and was comparable to other dupilumab dosing regimens with respect to safety parameters. Therefore the 300 mg qw dose will be the highest dose regimen studied in the phase 3 program, and was the original dosing regimen selected for this phase 3, long-term safety study.

Since initiation of this trial, multiple AD, placebo-controlled, phase 3 studies of dupilumab compared with placebo have been unblinded. In those studies, 300 mg dupilumab qw and q2w dose regimens were shown to have superior efficacy compared with control, as well as an acceptable safety profile. There were no statistically significant differences in efficacy between 300 mg qw and 300 mg q2w. The dose used in this Open-Label Extension (OLE) study remained 300 mg qw as this was the highest dose for which we planned to seek registration. The dosing regimen of dupilumab 300 mg qw was changed to q2w to match the dosing regimen approved by various regulatory agencies, globally, for this patient population.

1.2.3. Rationale for the Sub-Study

The sponsor is implementing an improved manufacturing process for the dupilumab drug product. Analysis of data obtained via quality testing and extended protein characterization demonstrate that dupilumab obtained from the new process is comparable to dupilumab obtained from the current process. This clinical sub-study is designed to demonstrate clinical evidence of the safe use in patients with AD when switched from the current dupilumab drug product to the new dupilumab drug product.

As part of the sub-study, safety, pharmacokinetics (PK), and immunogenicity endpoints before and after switching to the new dupilumab drug product will be summarized and listed.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the long-term safety of dupilumab administered in adult patients with AD.

2.2. Secondary Objective

The secondary objective of the study is to assess the immunogenicity of dupilumab in adult patients with AD, in the context of re-treatment, and to monitor efficacy parameters associated with long-term treatment.

2.3. Sub-Study Objectives

The primary objective of the sub-study is to assess the safety of the new dupilumab drug product in adult patients with AD after switching from the current dupilumab drug product.

The secondary objectives of the sub-study are to evaluate systemic exposure and immunogenicity of the new dupilumab drug product in adult patients with AD.

3. STUDY DESIGN

3.1. Study Description and Duration

This is a multicenter, open-label extension study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD who have previously participated in controlled studies of dupilumab or have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized because of randomization closure.

Enrollment will take place at approximately 500 global study sites. After providing informed consent, patients will be assessed for study eligibility at the screening visit. The screening visit in this study may coincide with the last visit in the previous study, in which case assessments that are common to both studies will be performed only once.

A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg SC dupilumab qw starting on day 8. For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

Patients will return for visits as specified in Section 6. In order to minimize the amount of drug that patients need to store in their home between visits, some visits will be abbreviated for the primary purpose to receive additional drug supply. The study treatment duration will be up to 5 years. The end of study visit occurs at 84 days/12 weeks after the last dose. Patients who have completed their end of treatment visit as per amendment 7 will be permitted to resume treatment with study drug. Eligible patients who have completed the end of study visit as per amendment 7 will be permitted to re-enter the study if no more than 12 weeks have elapsed since their end of

study visit. The entry criteria for patients who re-enter the study are listed in Section 4.2.3. As of the date of issue of amendment 8, this study is closed to further enrollment.

Patients and/or caregivers who are willing and able to administer dupilumab doses outside the clinic will be trained on injecting study drug unless they had already been trained during their participation in the previous study. These patients will self-inject study drug (or have the drug administered by a caregiver) during weeks in which no clinic visit is scheduled. Safety, laboratory, and clinical assessments will be performed at specified clinic visits.

Patients who receive treatment with a prohibited or restricted medication will be discontinued from study drug for the duration of the prohibited treatment (plus 5 half-lives as applicable). Study treatment may be resumed only if approved by the medical monitor.

Patients who test positive for anti-drug antibodies (ADAs) at their last study visit (early termination or end of study) may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details and time points).

The study flow diagram for the main study is provided in Figure 1.

Figure 1: Study Flow Diagram

Screening		**Treatment Period**[b, c]									
	Baseline										
V1	V2	V3[e]	V4[e]	V5[e]	V6	V7[e]	V8	V9-V30[d]	V31[f g]-V43[h,i]	**V44/EOT[g,i]**	**EOS**
D-28 to D-1[a]	D1	W1	W2	W3	W4	W8	W12	W16-W148 (every 8 weeks)	(every 8 to 16 weeks)		12 weeks after last dose

[a] Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

[b] A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8. For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[c] Patients will be monitored at the study site for a minimum of 30 minutes at the baseline visit.

[d] Visits 10, 12, 14, and 16 have been removed per amendment 6. This yields a schedule in which visits are 8 weeks apart from week 16 through week 48. The week 48 visit is followed by a visit at 52 weeks; then visits occur every 8 weeks thereafter up to and including the end of treatment [EOT] visit).

[e] Visits 3, 4, 5, and 7 were removed per amendment 6.

[f] Patients who have completed their EOT visit as per amendment 7 may resume treatment with study drug at the next scheduled visit they would have attended if they had not had an EOT visit.

[g] Patients who have completed their end of study (EOS) visit as per amendment 7 will be re-evaluated for eligibility at a trial Re-Entry visit. Patients eligible to re-enter the trial may resume treatment at the next scheduled visit they would have attended if they had not completed the study. Patients are not eligible to re-enter the trial if more than 12 weeks have elapsed since their EOS visit.

[h] Visits 26, 28, 32, 34, 36, 38, 40, and 42 were removed per amendment 9.

[i] Approximately 50 patients who have not completed visit 44 (EOT) prior to implementation of amendment 10 will be asked to participate in a sub-study using the new dupilumab product. Eligible patients will enter the sub-study at either visit 41, 43, or 44 of the main study. This optional sub-study requires a separate consent.

Sub-Study:

Approximately 50 patients who are participating in the current OLE study and have not completed the end of treatment visit (visit 44) prior to the implementation of amendment 10 will be asked to participate in the sub-study. After providing informed consent, eligible patients will enter the sub-study at either visit 41, 43, or 44 of the main study and have study treatment switched from the current dupilumab drug product to the new dupilumab drug product at sub-study visit 1a. Dupilumab dosing will remain 300 mg SC q2w, and patients will be treated with the new dupilumab drug product 300 mg SC q2w for at least 12 weeks (some patients may be treated for 24 weeks). The end of study visit for patients participating in the sub-study will be 84 days (12 weeks) after the last dose using the new dupilumab drug product. Patients who enter the sub-study from either visit 43 or visit 44 of the main study will have the duration of their study treatment increased by 4 or 12 weeks, respectively.

The study flow diagram for patients in the sub-study is provided in Figure 2.

Figure 2: Sub-Study Flow Diagram

Study Procedures	**Sub-Study Treatment Period**				**End of Study**[4]
Sub-Study Visit (V)	V1a[1,2]	V2a	V3a	V4a[3]	
Sub-Study Week (Wk)	Wk 0	Wk4	Wk12	Wk 24	Last Dose + 12Wk

Abbreviations: V=visit; Wk=week.

[1] This optional sub-study requires a separate consent.

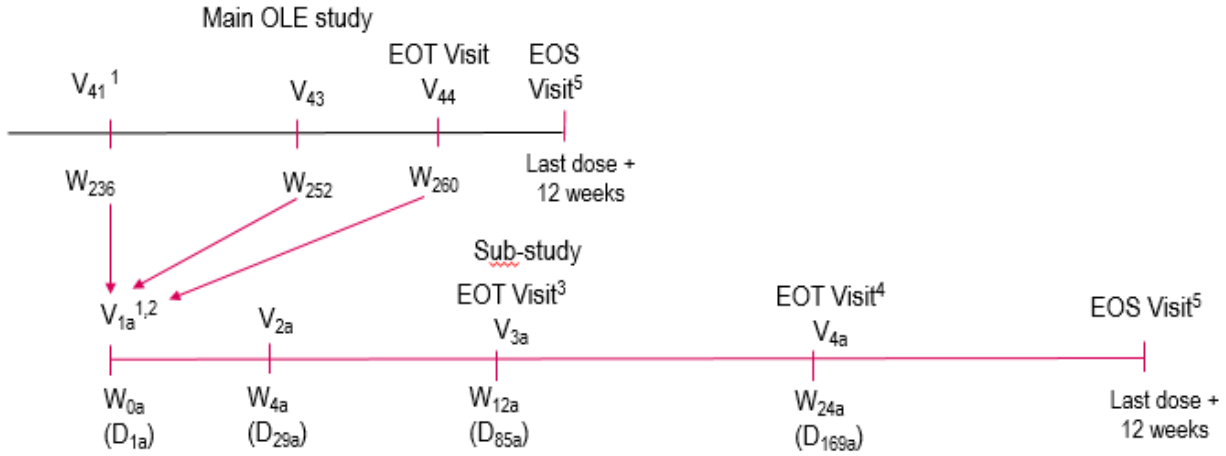
[2] Any redundant procedures with the main study visit will only be performed once.

[3] Applies only to patients in the sub-study who switched to the new dupilumab drug product at visit 41 of the main study. All other patients in the sub-study complete the new dupilumab drug product treatment period at sub-study visit 3a.

[4] The end of study (EOS) visit occurs 12 weeks after the last dose of dupilumab.

The relationship between the study visit schedules in main OLE study and the sub-study is shown in Figure 3.

Figure 3: Relationship Between Visit Schedules in Main OLE Study and Sub-Study



Abbreviations: D=day; EOS=end of study; EOT=end of treatment; SOE=schedule of events; V=visit; W=week.

[1] Patients will enter the sub-study at various time points during participation in the main OLE study (V41, V43, or V44). At V41, V43, or V44 (which will vary from patient to patient but should be a scheduled in-clinic visit), patients who are willing to participate in the sub-study and who are eligible, will enter V1a of the sub-study. At V1a, patients should have assessments and procedures performed as per both the SOE of the OLE study (V41, V43, or V44) as well as the sub-study (V1a) (any redundant procedures will only be performed once). This optional sub-study requires a separate consent. Patients who do not enter the sub-study will continue to follow the SOE for the main study.

[2] The first new dupilumab drug product administration should occur 14 days (±3 days; preferably ±1 day) after the previous administration of the current dupilumab drug product in the main study.

[3] For patients who began treatment with the new dupilumab drug product at V43 or V44 of the main study, the last dose of the new dupilumab drug product will be administered at sub-study V3a.

[4] V4a only applies to patients who switched to the new dupilumab drug product at V41 of the main study. The last dose for these patients will be administered at sub-study V4a.

[5] The EOS visit occurs 12 weeks after the last dose of dupilumab in either the main OLE study or the sub-study. The same EOS assessments are performed for patients receiving the current dupilumab drug product or the new dupilumab drug product.

3.2. End of Study Definition

The end of study is defined as the last visit for the last patient.

3.3. Planned Interim Analysis

No interim analysis is planned for this open-label study. Summaries of the data may be provided for regulatory agency interactions and for other clinical program purposes.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

The study is open to patients who participated in controlled and/or short term dupilumab clinical trials or patients who have been screened for a phase 3 study (R668-AD-1334 or R668-AD-1416), but could not be randomized due to randomization closure. Based on the numbers of patients enrolled or screened in the antecedent dupilumab studies, it is currently anticipated that approximately 2500 patients will be enrolled in this global study. Institutional Review Boards (IRBs)/Ethics Committees (ECs) will be notified if there is more than 25% greater participation than currently anticipated.

Sub-Study:

Approximately 50 patients who are participating in the current study and have not completed the end of treatment visit (ie, visit 44) prior to the implementation of amendment 10 will be invited to participate in the sub-study. After providing signed informed consent, eligible patients will enter the sub-study at either visit 41, 43, or 44 of the main study and have study treatment switched from the current dupilumab drug product to the new dupilumab drug product at sub-study visit 1a.

4.2. Study Population

The target population includes adult patients (≥18 years of age) with AD who participated in a prior dupilumab clinical study.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Participation in a prior clinical trial of dupilumab for AD and met one of the following:
    a. Received study treatment and adequately completed the assessments required for both the treatment and follow-up periods of the parent studies (except studies listed in b) as defined in the parent protocols; specifically, patients must complete the primary endpoint visit and at least 50% of the scheduled in-clinic visits and at-home assessments*). Additionally, patients who discontinued a parent study prematurely (ie, patients who did not complete the protocol-defined end-of-study visit) cannot enroll into this open-label extension study before the date when the end-of-study visit would have normally occurred. Completion of the entire follow-up period is not required for parent studies where the protocol specifically allows for an earlier transition into the open-label extension, in which case these requirements apply up to the point of this early transition.

    * For at-home assessments (eg, patient reported outcomes by interactive voice response system [IVRS] calls), patients who completed less than 50% of the assessments may be eligible if technical issues (eg, IVRS system malfunction) or other documented objective circumstances contributed to missing assessments, subject to approval by the medical monitor.

b. Received study treatment in any dupilumab AD study that has completed last patient last visit irrespective of duration of participation, provided that patients complied with the instructions received during the study, as assessed by the investigator.

c. Underwent screening in R668-AD-1334 (Liberty AD SOLO 1) or R668-AD-1416 (Liberty AD SOLO 2), but could not be randomized due to randomization closure.

These patients must have met the inclusion criteria for the Liberty AD SOLO studies that were applicable at the screening visit, specifically:

- Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 3 years before the screening visit
- Eczema Area and Severity Index (EASI) score ≥16 at the screening visit
- Investigator's Global Assessment (IGA) score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening visit
- ≥10% body surface area (BSA) of AD involvement at the screening visit
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks)*

  * With the clarification notes provided in the SOLO protocols.

  For these patients, the following criteria must also apply at the baseline visit in this open-label study:

- EASI score ≥16
- IGA score ≥3
- ≥10% BSA of AD involvement

2. Must be ≥18 years of age at screening
3. Willing and able to comply with all clinic visits and study-related procedures
4. Able to understand and complete study-related questionnaires
5. Provide signed informed consent

Sub-Study:

Additional inclusion criteria that must be met before a patient can enter the sub-study and switch to the new dupilumab drug product (per amendment 10) are provided in Section 4.2.4.1.

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Patients who, during their participation in a previous dupilumab clinical trial, developed a serious adverse event (SAE) deemed related to dupilumab*, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.
2. Patients who, during their participation in a previous dupilumab clinical trial, developed an AE that was deemed related to dupilumab* and led to study treatment discontinuation, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.
3. Conditions in the previous dupilumab study consistent with protocol-defined criteria for permanent study drug discontinuation, if deemed related to dupilumab* or led to investigator - or sponsor-initiated withdrawal of patient from the study (eg, non-compliance, inability to complete study assessments, etc.), unless such conditions are considered resolved and of no further consequence – subject to medical monitor review and approval.

   * Note for exclusion criteria # 1, 2, and 3: In studies that are still blinded, conditions deemed related to the study treatment will be considered related to dupilumab.
4. Treatment with an investigational drug, other than dupilumab, within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit.
5. Treatment with immunosuppressive/immunomodulating drugs (eg, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, JAK inhibitors) within 5 half-lives before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment in the current study.
6. Treatment with immunomodulating biologics, other than dupilumab, within 5 half-lives (if known) or 16 weeks (whichever is longer) before the first dose in the open-label extension study.
7. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit.
8. Planned or anticipated use of any prohibited medications and procedures during study treatment.
9. Any active infection requiring systemic treatment; patients with such infection must have their infection resolved at least 1 week before baseline to be eligible to enroll in the study.
10. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency as judged by the investigator.
11. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity (HIV testing is not required at screening for patients with a negative HIV result within the past 1 year prior to baseline).

12. Known history of positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody. If a patient has a documented negative result for any of these tests within 1 year of baseline, that particular test is not required at screening. Patients with isolated positive HBcAb or with positive hepatitis C antibody may undergo additional tests and consultations, and may enter the study only if active hepatitis B infection or carrier status has been definitively ruled out, subject to medical monitor's written approval.
13. History of clinical endoparasite infection within 12 months of the baseline visit, other than treated vaginal trichomoniasis.
14. Presence of skin comorbidities that may interfere with study assessments.
15. History of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
16. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to patients with short life expectancy, patients with uncontrolled diabetes (HbA1c ≥9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, hepato-biliary, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents.
17. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
18. High risk of parasite infection, such as residence within or recent travel (within 12 months before the baseline visit) to areas endemic for endoparasitoses, where the circumstances are consistent with parasite exposure (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.), unless subsequent medical assessments (eg, stool exam, blood tests, etc.) have ruled out the possibility of parasite infection/infestation.
19. History of alcohol or drug abuse within 2 years before the screening visit.
20. Planned major surgical procedure during the patient's participation in this study.
21. Patient is a member of the investigational team or his/her immediate family.
22. Pregnant or breastfeeding women, or planning to become pregnant or breastfeed during the patient's participation in this study.

23. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception whenever engaging in heterosexual intercourse throughout the duration of the study and for 12 weeks after last dose of study drug. These include: hormonal contraceptives, intrauterine device (IUD), a double barrier method (eg, condom + diaphragm), or male partner with documented vasectomy. Additional requirements for acceptable contraception may apply in certain countries, based on local regulations. Investigators in these countries will be notified accordingly in a protocol clarification letter. Investigators who are uncertain about the acceptability of a specific contraceptive method should seek advice and approval from the medical monitor.

    * For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone (FSH) of ≥25 mU/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

Sub-Study:

Additional exclusion criteria that must be met before a patient can enter the sub-study and be switched to the new dupilumab drug product (per amendment 10) are provided in Section 4.2.4.2.

4.2.3. Entry Criteria for Patients Re-Entering the Study

A patient who meets any of the following criteria will not be permitted to re-enter the study:

1. Patients who, during their previous participation in this clinical trial, developed an SAE deemed related to dupilumab, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.
2. Patients who, during their previous participation in this dupilumab clinical trial, developed an AE that was deemed related to dupilumab and led to study treatment discontinuation, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.
3. Patients who became pregnant during their previous participation in this dupilumab clinical trial.
4. Patients who, during their previous participation in this trial, were prematurely withdrawn because of a protocol violation, poor compliance, or inability to complete required study assessments.
5. Known history of HIV infection or HIV seropositivity. HIV testing is required at re-entry for patients who have not been tested within 12 months prior to re-entry.

6. Known history of positive HBsAg, HBcAb, or hepatitis C antibody. Hepatitis testing is required at re-entry for patients who have not been tested within 12 months prior to re-entry. NOTE: Patients who are HBsAg negative and HBsAb positive are considered immune after a natural infection has cleared or they have been vaccinated against hepatitis B. Therefore, they are acceptable for the study. These patients will be allowed to re-enter the study, but will be followed using routine clinical and liver function tests, as well as periodic hepatitis B viral load testing during study treatment.
7. Treatment interruption for >12 months.
8. Treatment with an investigational drug other than dupilumab, within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to the re-entry visit.
9. Treatment with immunosuppressive/immunomodulating drugs (eg, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, JAK inhibitors) within 5 half-lives before the re-entry visit.
10. Treatment with immunomodulating biologics, other than dupilumab, within 5 half-lives (if known) or 16 weeks (whichever is longer) before the re-entry visit.
11. Treatment with a live (attenuated) vaccine within 12 weeks before the re-entry visit.
12. Any active infection requiring systemic treatment; patients with such infection must have their infection resolved at least 1 week before the re-entry visit.
13. Pregnant or breastfeeding women.
14. Women unwilling to use adequate birth control, if of reproductive potential and sexually active (see Exclusion Criterion 23 above for applicable definitions).
15. Any medical or psychological condition that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the patient as a result of his/her participation in the trial, may make the patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in the source documents.
16. More than 12 weeks have elapsed since the patient's end of study visit.

4.2.4. Entry Criteria for Sub-Study

Patients who are ongoing in the main study and who have not completed the end of treatment visit (ie, visit 44) and who meet the sub-study eligibility criteria below may enter the sub-study at their next scheduled visit (ie, visits 41, 43, or 44). This optional sub-study requires a separate consent.

Patients who fail eligibility criteria for participating in the sub-study under amendment 10 may not be rescreened.

4.2.4.1. Sub-Study Inclusion Criteria

1. Continuing in the treatment period of the main OLE study.
2. Demonstrated compliance with dupilumab therapy defined as having received at least 5 out of 6 injections of the current dupilumab drug product in the 12 weeks prior to switching to the new dupilumab drug product, and not missing the last 3 dupilumab Q2W SC injections prior to the week 0a visit of the sub-study.
3. The last current dupilumab drug product administration occurred on day -14 (±3 days) prior to the scheduled day for the switch to the new dupilumab drug product (sub-study week 0a visit). Note: The protocol allows a window of ±3 days, but recommends a window ±1 day.
4. Provide signed informed consent for participation in the sub-study using dupilumab derived from the improved manufacturing process.

4.2.4.2. Sub-Study Exclusion Criteria

1. Patients who have already completed the end of treatment visit (ie, visit 44) for the main study R668-AD-1225.

4.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, cure, and for administrative, or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who withdraw prematurely from the study will be asked to complete study assessments per Section 6.2.8.

4.4. Replacement of Patients

Patients will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

Dupilumab will be supplied in ready to use prefilled syringes (PFS) for SC administration of 300 mg at a concentration of 150 mg/mL.

Study treatment will begin on day 1 (baseline). Patients and/or caregivers who are willing and able to self-administer some dupilumab doses outside of the clinic will be trained on injecting study drug unless they had already been trained during their participation in the previous study. These patients will self-inject study drug (or have the study drug administered by a caregiver) during weeks in which no clinic visit is scheduled.

Patients who prefer to have the clinic staff administer each dose of study drug may have all injections administered in the clinic.

A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline). The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8. For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks. If these patients (or their caregivers) require injection training, a study staff member can administer the first of the 2 injections and the patient (or caregiver) can subsequently administer the second injection under the supervision of the clinic staff.

Patients who have either previously completed treatment or completed the study as per amendment 7 and who resume treatment under amendment 7 or 8 will receive a loading dose of 600 mg SC (two 300 mg doses administered on the same day) if more than 4 weeks has elapsed since their last dose of study drug.

In the sub-study, patients will receive the new dupilumab drug product 300 mg SC q2w.

The procedure for preparing and administering dupilumab will be provided in the pharmacy manual. Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and optionally upper arms, so that the same site is not injected for 2 consecutive weeks. To allow for adequate assessment of possible injection site reactions (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the patient (or caregiver). Patients will document/report compliance with self-injection of study drug in a patient dosing diary via IVRS/interactive web response system (IWRS).

5.2. Dose Modification and Study Drug Discontinuation Rules

5.2.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.2.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug will be asked to return to the clinic for early termination assessments, per Section 6.2.8.

5.2.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study drug dosing in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Pregnancy at any time during the study
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities that are judged to be related to dupilumab per criteria described in Section 7.3.2, such as:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - Confirmed (by 2 separate tests at least 2 weeks apart) alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3 x upper limit of normal (ULN) and total bilirubin >2 x ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5 x ULN (for more than 2 weeks)
- Inadequate efficacy:
  - Patients who show inadequate therapeutic response after at least 12 weeks of treatment with dupilumab will be discontinued from the study treatment based upon review of the case and joint decision by the investigator and medical monitor. For the purpose of this assessment, a review of efficacy will be triggered whenever patients fail to achieve and/or maintain EASI-25 (at least 25% improvement in the EASI score) at week 16, compared to the baseline score in the previous controlled and/or short-term study. Patients may also withdraw from the study at any time if they are not satisfied with the study treatment (see Section 4.3)
- Other reasons that may lead to the permanent discontinuation of study drug include:
  - Certain AEs deemed related to the study drug (eg, severe and prolonged ISRs)

5.2.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug must be discontinued in case of:

- Severe laboratory abnormalities (as noted in Section 5.2.2.1) where a causal relationship to dupilumab can be reasonably excluded (ie, an alternative cause is evident). In these cases, study treatment will be discontinued (at least 1 dose while the clinical circumstances are being assessed), but it may be resumed when the laboratory parameters normalize sufficiently. A decision to resume study treatment will be made jointly by the investigator and the medical monitor.

Study drug dosing may be temporarily discontinued in the event of:

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - Creatine phosphokinase (CPK) >10 x ULN, unless the increase can be clearly attributed to physical exertion and considered clinically inconsequential.
- Other intercurrent illnesses or major surgery
- Any severe infection; any bacterial or viral infection requiring systemic treatment and remaining unresolved after 2 weeks of appropriate treatment; any clinical helminth endoparasitosis; any opportunistic infection
- Treatment with a live (attenuated) vaccine. Study drug dosing will be suspended for at least 12 weeks. NOTE: If the need for live vaccination is known in advance, to the extent possible, stop study drug for 12 weeks prior to vaccination
- Treatment with systemic nonsteroidal immunosuppressive/immunomodulating medications (eg, cyclosporine, methotrexate, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors, biologic agents, etc)

After the condition leading to temporary discontinuation of study drug resolves and/or the laboratory abnormality leading to suspension of dosing normalizes sufficiently, study drug dosing may resume at the discretion of the principal investigator in consultation with the medical monitor. Similarly, study treatment may resume after the medication leading to suspension of dosing has been discontinued. A decision to temporarily discontinue study drug and/or to resume study drug dosing should be discussed with the medical monitor. Resumption of study drug will require the medical monitor's written approval. The investigator may discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor and will require the medical monitor's written approval.

5.3. Method of Treatment Assignment

Not applicable for this single-arm, open-label study.

5.4. Treatment Logistics and Accountability

5.4.1. Packaging, Labeling, and Storage

Study drug will be shipped open label and labeled with a unique reference number in accordance with local regulations. Study drug will be refrigerated at the site at a temperature of 2°C to 8ºC. Storage instructions will be provided in the pharmacy manual.

5.4.2. Supply and Disposition of Treatments

Study drug will be shipped to the site at regular intervals or as needed during the study via the IVRS/IWRS. Drug accountability will be performed at specified time points during the study by the site monitor (ie, interim site monitoring visits) and at the site close-out visit. Following drug reconciliation and documentation by the site monitor, all opened and unopened prefilled syringes (PFS) of study drug will be destroyed or returned to the sponsor or designee.

5.4.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.4.4. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

Patients will document/report compliance with self-injection of study drug in a patient dosing diary via IVRS/IWRS.

5.5. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

5.5.1. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 5.5.2, treatment with concomitant medications are permitted during the study. This includes treatment with contraceptives, basic skin care (cleansing and bathing including bleach baths), emollients, topical anesthetics, antihistamines, topical and systemic anti-infective medications for any duration, topical calcineurin inhibitors, topical corticosteroids, and systemic corticosteroids.

Cytochrome P450: The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized.

However, IL-4 was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (Abdel-Razzak 1993, Christensen 2012). Human peripheral blood mononuclear cells incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (Liptrott 2009).

Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, investigators are cautioned to monitor clinical and laboratory signs that might indicate a potential drug-drug interaction in all patients receiving dupilumab concomitantly with narrow therapeutic index medications that are metabolized by CYP450. This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal, if needed.

5.5.2. Prohibited and Restricted Medications

Concomitant treatment with the following medications is prohibited during the study. These medications should generally be avoided, but if they are medically necessary (eg, as a rescue treatment for intolerable AD symptoms or to manage serious intercurrent conditions), they may be administered while the study drug is discontinued.

- Treatment with nonsteroidal systemic immunosuppressive medications (including, but not limited to, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or other immunomodulating biologics*)
- Treatment with an investigational drug* (other than dupilumab)

- Live (attenuated) vaccines**

Chickenpox (Varicella)
FluMist-Influenza
Intranasal influenza
Measles (Rubeola)
Measles-mumps-rubella (MMR) combination
Measles-mumps-rubella-varicella (MMRV) combination
Mumps
Oral polio (Sabin)
Oral typhoid
Rubella
Smallpox (Vaccinia)
Yellow fever
Bacillus-Calmette–Guérin (BCG)
Rotavirus
Varicella Zoster (shingles)

* Patients who receive an immunomodulating biologic or investigational drug will be discontinued from study drug for the duration of treatment with these medications, plus 5 half-lives (if known) or 16 weeks, whichever is longer.

** In the case of live vaccines, study treatment should optimally be stopped 12 weeks before vaccine administration and may not resume sooner than 12 weeks after vaccine administration.

In all cases, the resumption of study treatment must be approved by the medical monitor.

Patients who discontinue study treatment permanently will be asked to complete the assessments of the early termination and end of study visits.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit for the main study in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. After providing informed consent for the sub-study, which is using the new dupilumab drug product, eligible patients are to follow the assessments and procedures in Table 8.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: Schedule of Events – Visits 1 through 8 (Week 12)

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3[m]**	**V 4[m]**	**V 5[m]**	**V 6**	**V 7[m]**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1[a]**	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Screening/Baseline:								
Informed consent	X							
Inclusion/Exclusion	X	X						
Medical History/Demographics	X	X						
Training on IVRS/IWRS		X						
Treatment:								
Injection training/observation		X				X		
Administer study drug[c]		X[b]	⋯	⋯	⋯	⋯	⋯	→
Patient dosing diary[d]		X				X		X
Study drug dispensation/account[e]		X				X		X
Con meds/procedures	X	X				X		
Efficacy:[f]								
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[i]		X ⋯				→ X ⋯		→
IGA, EASI	X	X				X		
POEM, DLQI, EQ-5D[g]		X						
Safety:[f]								
Weight	X	X						
Height	X	X						
Vital signs	X	X				X		
Physical examination		X						
Ophthalmology exam[k] (select sites and patients)		X				X		X
Adverse events[h]	X	X ⋯				→ X ⋯		→ X

Study Procedures	**Screening***	**Baseline**	**Treatment Period**					
Visit (V)	**V 1**	**V 2**	**V 3[m]**	**V 4[m]**	**V 5[m]**	**V 6**	**V 7[m]**	**V 8**
Week (Wk)			**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**
Day (D)	**-28 to -1[a]**	**D 1**	**D 8**	**D 15**	**D 22**	**D 29**	**D 57**	**D 85**
Visit Window (d)			+/-2d	+/-2d	+/-2d	+/-3d	+/-3d	+/-3d
Laboratory Testing:[f]								
Hematology, Chemistry	X	X						
Pregnancy test, WOCBP only	Serum	Urine[l]				Urine[l]		Urine[l]
HIV screening[j]	X							
HBsAg, HBcAb, hepatitis C antibody[j]	X							
Drug Concentration/PK and Anti-drug Antibody Testing:[f]								
Drug concentration/PK sample		X						
ADA sample		X						

*Note: The screening visit in this study may coincide with the last visit in the previous study. Assessments that are common to both studies will be performed only once.

a. Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor.

b. A loading dose of 600 mg SC (two 300 mg doses administered on the same day) dupilumab will be administered on day 1 unless the patient has received a dose of dupilumab in the 4 weeks prior to baseline. If the patient has received a dose of dupilumab in the past 4 weeks, then they will receive a single 300 mg dose at baseline. The first dose should be at least 1 week after the last dose in the previous study, and then 300 mg dupilumab qw starting on day 8. In addition to the predose assessments, vital signs and AEs will be assessed at 30 (+/- 10) minutes postdose.

c. Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

d. If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic

e. Starting at visit 2, study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

f. To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.

g. The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.

h. In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

i. Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

j. Any of these tests is required only for patients who have not had a documented negative result for the respective test within 1 year prior to baseline (the negative HIV result must be from a parent study).

k. An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit, which can take place at any time between the screening and baseline visits, inclusive.

l. Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

m. Visits 3, 4, 5, and 7 were removed per amendment 6.

Table 2: Schedule of Events – Visits 9 (Week 16) through 18 (Week 52)

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10** [j]	**V 11**	**V 12** [j]	**V 13**	**V 14** [j]	**V 15**	**V 16** [j]	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:										
Administer study drug [a]	X									
Patient dosing diary [b]	X		X		X		X		X	X
Study drug dispensation/account [c]	X		X		X		X		X	X
Con meds/procedures	X				X				X	
Efficacy: [d]										
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X								X	
IGA, EASI	X								X	
POEM, DLQI, EQ-5D [e]									X	
Safety: [d]										
Weight									X	
Vital signs	X				X				X	
Ophthalmology exam [i] (select sites and patients)	X				X				X	
Adverse events [f]	X									X
Laboratory Testing: [d]										
Hematology, Chemistry	X								X	
Pregnancy test, WOCBP only[h]										

Study Procedures	**Treatment Period**									
Visit (V)	**V 9**	**V 10**[j]	**V 11**	**V 12**[j]	**V 13**	**V 14**[j]	**V 15**	**V 16**[j]	**V 17**	**V 18**
Week (Wk)	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Day (D)	**D 113**	**D 141**	**D 169**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Drug Concentration and Antibody Testing:[d]										
Drug Concentration sample									X	
ADA sample									X	

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c.] Study drug will be dispensed to the patient for all doses that will be administered before the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.

[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.

[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[g.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[h.] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

[j.] Visits 10, 12, 14, and 16 have been removed per amendment 6.

Table 3: Schedule of Events – Visits 19 (Week 60) through 24 (Week 100)

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X ·····	·····	·····	·····	·····	·····
Patient dosing diary[b]	X ·····	·····	·····	·····	·····	X
Study drug dispensation/account[c]	X ·····	·····	·····	·····	·····	X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[g]	X •·····	·····	·····	·····	·····	X •·····
IGA, EASI	X					X
POEM, DLQI, EQ-5D [e]						X
Safety: [d]						
Weight	X		X			X
Vital signs	X		X	X	X	X
Ophthalmology exam[i] (select sites and patients)	X		X		X	
Adverse events[f]	X ·····	·····	·····	·····	·····	X
Laboratory Testing: [d]						
Hematology, Chemistry						X
Pregnancy test, WOCBP only[h]	·····	·····	·····	·····	·····	·····

Study Procedures	**Treatment Period**					
Visit (V)	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**
Week (Wk)	**Wk 60**	**Wk 68**	**Wk 76**	**Wk 84**	**Wk 92**	**Wk 100**
Day (D)	**D 421**	**D 477**	**D 533**	**D 589**	**D 645**	**D 701**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Drug Concentration and Antibody Testing:[d]						
Drug Concentration sample						X
ADA sample						X

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d.] To be collected before the injection of study drug. The order of the assessment should be questionnaires first, followed by laboratory evaluations.

[e.] The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available.

[f.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[g.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[h.] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[i.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

Table 4: Schedule of Events – Visits 25 (Week 108) through Visit 30 (Week 148)

Study Procedures	**Treatment Period**					
Visit (V)	**V 25**	**V 26**[i]	**V 27**	**V 28**[i]	**V 29**	**V 30**
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X ●····				····→	X
Patient dosing diary[b]	X ●····				····→	X
Study drug dispensation/account[c]	X ●····				····→	X
Con meds/procedures	X		X		X	
Efficacy:[d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X ●····				····→	X
IGA, EASI			X			
Safety: [d]						
Weight	X		X			
Vital signs	X		X		X	X
Ophthalmology exam[h] (select sites and patients)	X		X		X	
Adverse events[e]	X ●····				····→	X
Laboratory Testing: [d]						
Hematology, Chemistry						X
Pregnancy test, WOCBP only[g]	X ●····				····→	X
HIV screening						
HBsAg, HBcAb, hepatitis C antibody						

Study Procedures	**Treatment Period**					
Visit (V)	**V 25**	**V 26** [i]	**V 27**	**V 28** [i]	**V 29**	**V 30**
Week (Wk)	**Wk 108**	**Wk 116**	**Wk 124**	**Wk 132**	**Wk 140**	**Wk 148**
Day (D)	**D 757**	**D 813**	**D 869**	**D 925**	**D 981**	**D 1037**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample			X			
ADA sample			X			X

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d.] To be collected before the injection of study drug.

[e.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[f.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[g.] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[h.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

[i.] Visits 26 and 28 were removed per amendment 9.

Table 5: Schedule of Events – Visits 31 (Week 156) through Visit 36 (Week 196)

Study Procedures	**Treatment Period**					
Visit (V)	**V 31**	**V 32** [i]	**V 33**	**V 34** [i]	**V 35**	**V 36** [i]
Week (Wk)	**Wk 156**	**Wk 164**	**Wk 172**	**Wk 180**	**Wk 188**	**Wk 196**
Day (D)	**D 1093**	**D 1149**	**D 1205**	**D 1261**	**D 1317**	**D 1373**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:						
Administer study drug[a]	X	●····	····	····	····→	X
Patient dosing diary[b]	X	●····	····	····	····→	X
Study drug dispensation/account.[c]	X	●····	····	····	····→	X
Con meds/procedures	X		X		X	
Efficacy: [d]						
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	●···· X	····	····	····→		X
IGA, EASI	X					
Safety: [d]						
Weight	X		X		X	
Vital signs	X		X		X	
Ophthalmology exam[h] (select sites and patients)	X		X		X	
Adverse events[e]	X ●····	····	····	····→		X
Laboratory Testing: [d]						
Hematology, Chemistry						
Pregnancy test, WOCBP only[g]		●····	····	····	····→	
HIV Screening						
HBsAg, HBcAb, hepatitis C antibody						

Study Procedures	**Treatment Period**					
Visit (V)	**V 31**	**V 32** [i]	**V 33**	**V 34** [i]	**V 35**	**V 36** [i]
Week (Wk)	**Wk 156**	**Wk 164**	**Wk 172**	**Wk 180**	**Wk 188**	**Wk 196**
Day (D)	**D 1093**	**D 1149**	**D 1205**	**D 1261**	**D 1317**	**D 1373**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Drug Concentration and Antibody Testing: [d]						
Drug Concentration sample						
ADA sample			X			

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d.] To be collected before the injection of study drug.

[e.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[f.] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[g.] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[h.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

[i.] Visits 32, 34, and 36 were removed per amendment 9.

Table 6: Schedule of Events – Visits 37 (Week 204) through Visit 43 (Week 252)

Study Procedures	Treatment Period						
Visit (V)	**V 37**	**V 38** [i]	**V 39**	**V 40** [i]	**V 41**[j]	**V 42** [i]	**V 43**[j]
Week (Wk)	**Wk 204**	**Wk 212**	**Wk 220**	**Wk 228**	**Wk 236**	**Wk 244**	**Wk 252**
Day (D)	**D 1429**	**D 1485**	**D 1541**	**D 1597**	**D 1653**	**D 1709**	**D 1765**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Treatment:							
Administer study drug [a]	X						X
Patient dosing diary [b]	X						X
Study drug dispensation/account [c]	X						X
Con meds/procedures	X		X		X		X
Efficacy:[d]							
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	X						X
IGA, EASI	X						
Safety:[d]							
Weight	X		X		X		X
Vital signs	X		X		X		X
Ophthalmology exam[h] (select sites and patients)	X		X		X		X
Adverse events[e]	X						X
Laboratory Testing:[d]							
Hematology, Chemistry	X						
Pregnancy test, WOCBP only[g]	X						
HIV Screening							
HBsAg, HBcAb, hepatitis C antibody							

Study Procedures	**Treatment Period**						
Visit (V)	**V 37**	**V 38** [i]	**V 39**	**V 40** [i]	**V 41**[j]	**V 42** [i]	**V 43**[j]
Week (Wk)	**Wk 204**	**Wk 212**	**Wk 220**	**Wk 228**	**Wk 236**	**Wk 244**	**Wk 252**
Day (D)	**D 1429**	**D 1485**	**D 1541**	**D 1597**	**D 1653**	**D 1709**	**D 1765**
Visit Window (d)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d
Drug Concentration and Antibody Testing:[d]							
Drug Concentration sample							
ADA sample			X				

[a.] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b.] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c.] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d.] To be collected before the injection of study drug.

[e.] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[f.] Patients will be trained on using the IVRS/IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[g.] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[h.] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit

[i.] Visits 38, 40, and 42 were removed per amendment 9.

[j] Patients who have not completed visit 44 (EOT) prior to implementation of amendment 10 will be asked to participate in a sub-study using the new dupilumab drug product. Eligible patients will enter the sub study at either visit 41, 43, or 44 of the main study. Any redundant procedures between the main study (eg, visit 41, 43, or 44) and the sub-study (eg, visit 1a) will only be performed once. This optional sub-study requires a separate consent.

Table 7: Schedule of Events – End of Treatment, End of Study, Early Termination, Unscheduled Visit, and Re-entry Visit

Study Procedures	**End of Treatment**	**End of Study [m]**	**Early Termination**	**Unscheduled Visit [j]** (if applicable)	**Re-entry Visit [r]** (for patients who re-enter the study)
Visit (V)	**V 44[s]**				
Week (Wk)	**260**	**Last dose +12Wk**			
Day (D) Visit Window (d)	**D 1821** +/-3d	**Last dose +84D** +/-30d			
Treatment:					
Inclusion/Exclusion (Re-entry)					X
Informed Consent (Re-entry)					X
Demographics (Re-entry)					X
Administer study drug[a]	X				
Patient dosing diary[b]	X		X		
Study drug dispensation/account[c]	X[n]		X	X	
Con meds/procedures	X	X	X	X	X
Efficacy: [d]					
Patient Assessment of Pruritus Intensity via IVRS/IWRS (weekly)[f]	•·····	·····→	X[f]	X[h]	
IGA, EASI	X	X	X	X	
Safety: [d]					
Weight	X	X	X	X	
Vital signs	X	X	X	X	
Ophthalmology exam[k] (select sites and patients)		X		X[l]	
Adverse events[e]	X	X	X	X	X
Laboratory Testing: [d]					
Hematology, Chemistry	X			X	X[o]
Pregnancy test, WOCBP only[g]	Urine Monthly	•·····	·····→	X	Serum[p]
HIV screening				X	X[q]
HBsAg, HBcAb, hepatitis C antibody				X	X[q]

Study Procedures	**End of Treatment**	**End of Study** [m]	**Early Termination**	**Unscheduled Visit** [j] (if applicable)	**Re-entry Visit** [r] (for patients who re-enter the study)
Visit (V)	**V 44**[s]				
Week (Wk)	**260**	**Last dose +12Wk**			
Day (D) Visit Window (d)	**D 1821** +/-3d	**Last dose +84D** +/-30d			
Drug Concentration and Antibody Testing: [d]					
Drug Concentration sample	X	X	X	X	
ADA sample	X	X[i]	X[i]	X	

[a] Study drug will be administered weekly, either in the clinic or outside the clinic (self-administration or administration by a care provider). For patients who have not completed the study prior to the implementation of amendment 9, study drug dosing will change from dupilumab 300 mg weekly to every 2 weeks.

[b] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.

[c] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.

[d] To be collected before the injection of study drug.

[e] In the event the patient experiences a visible ISR at any clinic visit, the clinical site may photograph the ISR and complete the ISR worksheet.

[f] Patients will be trained on using the IVRS /IWRS at the baseline visit, and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.

[g] Patients will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

[h] If the call was performed on the patient's weekly schedule, then it will not need to be repeated.

[i] Patients who test positive for ADA at their last study visit (early termination visit or end of study visit) may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details and time points).

[j] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

[k] An acceptable window for performing ophthalmology exams is within +/- 7 days of the visit date. This does not apply to the ophthalmology exam conducted at the baseline visit.

[l] Patients who experience AEs consistent with conjunctivitis or other superficial inflammation of the eye (blepharitis, keratitis, etc) should undergo additional (unscheduled) ophthalmology exams to allow accurate diagnosis and adequate treatment.

[m] If the end of study assessments cannot be completed on the scheduled date (ie, 12 weeks after the last dose of dupilumab), a late visit is acceptable and is preferable to foregoing these assessments altogether; this visit should be conducted as close as possible to the scheduled date.

[n] Only study drug accountability takes place at this visit.

[o] Sample will be collected only if the last sample was not collected within 12 months.

[p] Serum pregnancy test must be negative before dosing.

[q] Testing is required at re-entry for patients who have not been tested within 12 months prior to re-entry.

[r] Patients who have completed the end of study visit as per amendment 7 and who are eligible to resume treatment may re-enter the trial at the next scheduled visit they would have attended if they had not completed the study; the next visit should be scheduled within 7 days of the re-entry visit. Patients are not eligible to re-enter the trial if more than 12 weeks have elapsed since their end of study visit.

[s] Patients who have not completed visit 44 (EOT) prior to implementation of amendment 10 will be asked to participate in a sub-study using the new dupilumab drug product. Eligible patients will enter the sub study at either visit 41, 43, or 44 of the main study. Any redundant procedures between the main study (eg, visit 41, 43, or 44) and the sub-study (eg, visit 1a) will only be performed once. This optional sub-study requires a separate consent.

Table 8: Sub-Study Schedule of Events

Study Procedures	**Sub-Study Treatment Period**				**End of Study[d]**	**Early Termination**	**Unscheduled Visit[e]**
Sub-Study Visit (Va)	**V1a[a]**	**V2a**	**V3a[b]**	**V4a[c]**	**-**	-	-
Sub-Study Week (Wka)	**Wk 0a**	**Wk 4a**	**Wk 12a**	**Wk 24a**	**Last dose + 12 weeks**	-	**-**
Sub-Study Day (Da) Visit Window (d)	**D1a** ±3d[a]	**D29a** ±3d	**D85a** ±3d[f]	**D169a** ±3d	**Last dose + 84 days** ±3d	-	**-**
Screening/Baseline (Sub-Study)							
Informed consent (Sub-Study)	X						
Inclusion/exclusion criteria (Sub-Study)	X						
Treatment:							
Administer study drug[g]	X[a,h]	X	X	X			
Patient dosing diary[i]	X	X	X	X			
Study drug dispensation/account[j]	X	X	X[k]	X[l]		X	
Con meds/procedures	X	X	X	X	X	X	X
Efficacy:[m]							
Patient assessment of pruritus intensity via IVRS/IWRS (weekly)[n]	X	X	X	X	X	X	X[o]
IGA, EASI	X	X	X	X	X	X	X
Safety:[m]							
Weight	X				X	X	X
Vital signs	X	X	X	X	X	X	X
Ophthalmology exam (select sites and patients)[p]	X		X		X		X[q]
Adverse events	X	X	X	X	X	X	X
Laboratory Testing:[m]							
Hematology, chemistry	X		X		X		X
Pregnancy test, WOCBP only[r]	X	X	X	X	X	X	X
Drug Concentration and Antibody Testing:[m]							
Drug concentration sample	X		X	X	X	X	X
ADA sample	X		X	X	X	X	X

[a.] The first new dupilumab drug product administration at visit 1a should occur 14 days (±3 days) after the previous administration of the current dupilumab drug product in the main study. Although the protocol allows a visit window of ±3 days for visit 1a, the sponsor recommends a visit window ±1 day after the previous dose of the current dupilumab drug product. Any redundant procedures between the main study (eg, visit 41, 43, or 44) and the sub-study (eg, visit 1a) will only be performed once.

[b] For patients who begin treatment with the new dupilumab drug product after visit 41 of the main study, the last dose of the new dupilumab drug product will be administered at sub-study visit 3a.
[c] Visit only applies to patients who switch to the new dupilumab drug product at visit 41 of the main study.
[d] End of study visit occurs 12 weeks after the last dose of dupilumab. The same EOS assessments are performed for patients receiving the new dupilumab drug product as for the current dupilumab drug product.
[e] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.
[f] Sub-study visit 3a is to be conducted on sub-study day 85 (±3 days). Although the protocol allows for a visit window ±3 days, it is strongly recommended that visit 3a occurs 14 days (±1 day) after the self-injection of the new dupilumab drug product on sub-study day 71.
[g] Study drug will be administered every 2 weeks, either in the clinic or outside the clinic (self-administration or administration by a care provider).
[h] Patients will be monitored at the study site for a minimum of 30 minutes.
[i] If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic.
[j] Study drug will be dispensed to the patient for each dose that will be administered off-site between the current clinic visit and the next clinic visit. Patients will be instructed to return all study drug at each clinic visit.
[k] Drug accountability for patients who enter the sub-study at visits 43 or 44 of the main study. Drug accountability and dispensing for patients who entered the sub-study at visit 41 of the main study.
[l] Drug accountability for patients who enter the sub-study at visit 41 of the main study. This visit is not applicable for patients who enter the sub-study at visit 43 or 44 of the main study.
[m] To be collected before the injection of study drug.
[n] Patients will be retrained on using the IVRS/IWRS at the sub-study baseline visit (if needed) and will call into the system weekly to report the overall intensity of their pruritus over the previous week, and to record compliance with self-injection of study drug.
[o] If the call was performed on the patient's weekly schedule, then it will not need to be repeated.
[p] Only applies to patients who are in the ophthalmology sub-study in the main study (amendment 9). An acceptable window for performing ophthalmology exams is within ±7 days of the visit date.
[q] Patients who experience AEs consistent with conjunctivitis or other superficial inflammation of the eye (blepharitis, keratitis, etc) should undergo additional (unscheduled) ophthalmology exams to allow accurate diagnosis and adequate treatment.
[r] Women of childbearing potential (WOCBP) will be provided with a pregnancy test kit to take home for monthly urine sample testing in between clinic visits, or may choose to have the testing done at the study site.

6.2. Study Visit Descriptions

6.2.1. Visit 1/Screening/Day –28 to Day -1

After the patient has provided signed informed consent, he/she will be assigned a unique patient number, and the following information will be collected. Note: The screening visit in this study may coincide with the last visit in the previous study. Patients who fail screening or who fail to complete the baseline visit within 28 days of screening may be rescreened upon approval by the medical monitor. Assessments that are common to both studies will be performed only once:

- Inclusion/exclusion criteria
- Medical history
- Demographics (eg, date of birth, race, ethnicity)
- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Weight and height
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Serum hCG – for women of childbearing potential
  - HIV screening (not required if patients had a negative HIV test result in the parent study within 1 year prior to baseline)
  - HBsAg (not required if patients had a negative test result within 1 year prior to baseline)
  - HBcAb (not required if patients had a negative test result within 1 year prior to baseline)
  - Hepatitis C antibody (not required if patients had a negative test result within 1 year prior to baseline)

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Inclusion/exclusion criteria
- Medical history
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight and height
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Physical examination
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Injection training/observation (unless trained in the previous study)
- Study drug dispensation/accountability
- Administered only to the subset of patients who speak fluently the language in which the questionnaire can be translated:
  - POEM
  - DLQI
  - EQ-5D
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test– for women of childbearing potential
  - Drug concentration sample
  - ADA sample

- IVRS/IWRS training
- Administer study drug –600 mg loading dose (300 mg initial dose, followed by a 300 mg loading dose, unless last dose administered in the previous AD study is less than 4 weeks before their first dose in the current study, in which case administer 300 mg study drug)/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection: in addition to the predose assessments, vital signs and AE assessments will be done at 30 (+/- 10) minutes post-injection

6.2.2.2. Visit 3/Day 8/Week 1 (+/-2 Days)

This visit was removed per amendment 6.

6.2.2.3. Visit 4/Day 15/Week 2 (+/-2 Days)

This visit was removed per amendment 6.

6.2.2.4. Visit 5/Day 22/Week 3 (+/-2 Days)

This visit was removed per amendment 6.

6.2.2.5. Visit 6/Day 29/Week 4 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Laboratory samples:
  - Urine pregnancy test– for women of childbearing potential
- Injection training/observation (unless trained in the previous study)
- Administer study drug
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability

6.2.2.6. Visit 7/Day 57/Week 8 (+/-3 Days)

This visit was removed per amendment 6.

6.2.2.7. Visit 8/Day 85/Week 12 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Ophthalmology exam (select sites and patients)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.8. Visit 9/Day 113/Week 16 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.9. Visit 10/Day 141/Week 20 (+/-3 Days)

This visit was removed per amendment 6.

6.2.2.10. Visit 11/Day 169/Week 24 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.11. Visit 12/Day 197/Week 28 (+/-3 Days)

This visit was removed per amendment 6.

6.2.2.12. Visit 13/Day 225/Week 32 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.13. Visit 14/Day 253/Week 36 (+/-3 Days)

This visit was removed per amendment 6.

6.2.2.14. Visit 15/Day 281/Week 40 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.15. Visit 16/Day 309/Week 44 (+/-3 Days)

This visit was removed per amendment 6.

6.2.2.16. Visit 17/Day 337/Week 48 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Ophthalmology exam (select sites and patients)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Administered only to the subset of patients who speak fluently the language in which the questionnaire can be translated:
  - POEM
  - DLQI
  - EQ-5D

- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - ADA sample
  - Drug concentration sample
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.17. Visit 18/Day 365/Week 52 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.18. Visit 19/Day 421/Week 60 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI

- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Ophthalmology exam (select sites and patients)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.19. Visit 20/Day 477/Week 68 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.20. Visit 21/Day 533/Week 76 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Ophthalmology exam (select sites and patients)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential

- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.21. Visit 22/Day 589/Week 84 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.22. Visit 23/Day 645/Week 92 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Ophthalmology exam (select sites and patients)
- Study drug dispensation/accountability
- Administer study drug

6.2.2.23. Visit 24/Day 701/Week 100 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Administered only to the subset of patients who speak fluently the language in which the questionnaire can be translated:
  - POEM
  - DLQI
  - EQ-5D
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.24. Visit 25/Day 757/Week 108 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)

- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.25. Visit 26/Day 813/Week 116 (+/-3 Days)

This visit was removed per amendment 9.

6.2.2.26. Visit 27/Day 869/Week 124 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Ophthalmology exam (select sites and patients)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.2.27. Visit 28/Day 925/Week 132 (+/-3 Days)

This visit was removed per amendment 9.

6.2.2.28. Visit 29/Day 981/Week 140 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Ophthalmology exam (select sites and patients)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability
- Administer study drug

6.2.3. Visit 30/Day 1037/Week 148 (+/-3 Days)

The following information will be collected:

- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential
  - ADA sample
- Confirm that the patient completed/reported the dosing diary for each dose of study drug that was administered outside of the clinic
- Study drug accountability – return all PFS and study materials
- Administer study drug

6.2.4. Visit 31/Day 1093/Week 156 through Visit 43/Day 1765/Week 252 (+/-3 Days)

The study treatment duration will be up to 5 years. Visits 31 through 43 will occur approximately every 8 weeks until the end of treatment.

The following information will be collected:

- Concomitant medications/procedures: visit 31, 33, 35, 37, 39, 41, and 43.
- AEs
- Informed consent for the optional sub-study using the new dupilumab drug product: visit 41 or 43. See Section 6.2.6 for further information about procedures and assessments to be performed during the sub-study.

The following procedures and assessments will be conducted:

- IGA/EASI: visit 31, 37
- Weight: visit 31, 33, 35, 37, 39, 41, and 43
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate): visit 31, 33, 35, 37, 39, 41, and 43
- Ophthalmology exam (select sites and patients): visit 31, 33, 35, 37, 39, 41, and 43)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Hematology w/differential: visit 37
  - Serum chemistry: visit 37
  - Urine pregnancy test – for women of childbearing potential. Starting at visit 31 monthly until visit 43, urine pregnancy test must be negative before dosing.
  - ADA sample: visit 33 and 39
- Confirm that the patient completed/reported the dosing diary for each dose of study drug that was administered outside of the clinic
- Study drug dispensation/ accountability
- Administer study drug (weekly throughout the study)

6.2.5. End of Treatment Visit/Day 1821/Visit 44/Week 260 (+/-3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs
- Informed consent for the optional sub-study using the new dupilumab drug product: visit 44. See Section 6.2.6 for further information about procedures and assessments to be performed during the sub-study.

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- IGA
- EASI
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- Confirm that the patient completed/reported the dosing diary for each dose of study drug that was administered outside of the clinic
- Study drug accountability – return all PFS and study materials
- Administer study drug

6.2.6. Sub-Study Treatment Period

Patients who have provided written informed consent to participate in the sub-study using the new dupilumab drug product (per amendment 10) will have the following assessments and procedures performed. Patients who enter the sub-study from either visit 43 or visit 44 of the main study will have the duration of their study treatment increased by 4 or 12 weeks, respectively.

6.2.6.1. Sub-Study Visit 1a/Day 1a/Week 0a (±3 days)

Note: This visit should occur 14 days (±3 days) after the previous dose of current dupilumab drug product. Although, the protocol allows for a window of ±3 days, the sponsor recommends a window ±1 day for sub-study visit 1a after the previous dose of the current dupilumab drug product is administered.

Any redundant procedures between the main study (eg, visit 41, 43, or 44) and the sub-study (eg, visit 1a) will only be performed once.

The following information will be collected:

- Sign informed consent for sub-study
- Inclusion/exclusion criteria for switching to the new dupilumab drug product treatment (see Section 4.2.4)
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Study drug dispensation/accountability
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test– for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- Administer study drug (new dupilumab drug product)
  - Monitor the patient for a minimum of 30 minutes after the SC injection: in addition to the predose assessments, vital signs and AE assessments will be done at 30 (±10) minutes post-injection

6.2.6.2. Sub-Study Visit 2a/Day 29a/Week 4a (±3 days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Laboratory samples:
  - Urine pregnancy test– for women of childbearing potential
- Administer study drug (new dupilumab study drug product)
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug dispensation/accountability

6.2.6.3. Sub-Study Visit 3a/Day 85a/Week 12a (±3 days)

This visit should occur on sub-study day 85a (±3 days). Although the protocol allows a visit window of ±3 days, it is strongly recommended that visit 3a occurs 14 days (±1 day) after the self-injection of the new dupilumab drug product on sub-study day 71a.

The following information will be collected:

- AEs
- Concomitant medications/procedures;

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample

- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug accountability
- Administer study drug (new dupilumab drug product)
- Study drug dispensation (Note: patients who switched at visit 41 only)

6.2.6.4. Sub-Study Visit 4a/Day 169a/Week 24a (±3 days)

Note: This visit is only applicable to patients who switched to the new dupilumab drug product at visit 41 of the main study.

The following information will be collected:

- AEs
- Concomitant medications/procedures;

The following procedures and assessments will be conducted:

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- If needed, counsel patient on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the clinic
- Study drug accountability
- Administer study drug (new dupilumab drug product)

6.2.6.5. End of Study Visit (Last Dose+12 Weeks), Early Termination Visit, and Unscheduled Visits

Assessments and procedures to be performed at the end of study visit (last new dupilumab drug product dose+12 weeks) are described in Section 6.2.7, those for early termination visit in Section 6.2.8, and those for an unscheduled visit in Section 6.2.9. Except as noted, these assessments and procedures are the same as those done for patients who are receiving the current dupilumab drug product in the main study.

6.2.7. End of Study Visit (84 Days After Last Dose or 12 Weeks After Last Dose)

If the end of study assessments cannot be completed on the scheduled date (ie, 12 weeks after the last dose of dupilumab), a late visit is acceptable and is preferable to foregoing these assessments altogether; this visit should be conducted as close as possible to the scheduled date. Except as noted, the same end of study assessments are performed for patients receiving the current dupilumab drug product or new dupilumab drug product.

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
  - Hematology w/differential (patients in sub-study only)
  - Serum chemistry (patients in sub-study only)

6.2.8. Early Termination Visit

Patients who withdraw from the study will be asked to complete 2 more visits: once for early termination assessments, as described below, and again at 12 weeks after the last dose of dupilumab, for end of study assessments (Section 6.2.7). These visits are applicable to patients receiving the current dupilumab drug product or the new dupilumab drug product.

The following information will be collected:

- Confirm that the patient completed/reported the dosing diary for each dose of study drug that was administered outside of the clinic
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- IGA
- EASI
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly)
- Laboratory samples:
  - Urine pregnancy test – for women of childbearing potential
  - Drug concentration sample
  - ADA sample
- Study drug accountability – return all PFS and study materials

6.2.9. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

The following information will be collected:

- Study drug accountability
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Ophthalmology exam (select sites and patients)
- IGA
- EASI
- Patient assessment of pruritus intensity via IVRS/IWRS (weekly) (not to be repeated if performed on the patient's weekly schedule)
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urine pregnancy test – for women of childbearing potential (to be performed only if coincides with the patient's weekly schedule, or with the monthly pregnancy test)
  - HIV screening

- HBsAg, HBcAb, hepatitis C antibody
- Drug concentration sample
- ADA sample

6.2.10. Re-entry Visit (Main Study Only)

Patients who have completed their end of study visit of the main study as per amendment 7 will have their re-entry visit into the main study within 12 weeks of their end of study visit. Patients are not eligible to re-enter the trial if more than 12 weeks have elapsed since their end of study visit. This re-entry visit does not apply to the new dupilumab drug product sub-study.

Note: Medical history will not be collected for patients re-entering the study.

The following information will be collected:

- Inclusion/exclusion criteria
- Informed consent
- Demographics (eg, date of birth, race, ethnicity)
- Concomitant medications/procedures
- AEs

The following procedures and assessments will be conducted:

- Laboratory samples:
  - Hematology w/differential (sample will be collected only if the last sample was not collected within 12 months)
  - Serum chemistry (sample will be collected only if the last sample was not collected within 12 months)
  - HIV screening (required at re-entry for patients who have not been tested within 12 months prior to re-entry)
  - HBsAg, HBsAb, HBcAb, hepatitis C antibody (required at re-entry for patients who have not been tested within 12 months prior to re-entry)
  - Serum pregnancy test – for women of childbearing potential (serum pregnancy test must be negative before dosing)

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

Assessments performed only at the screening and/or baseline visit include medical history, medication history, physical examination, and demographics.

6.3.1.1. Patient Training on the Interactive Voice Response System

Patients will be trained on using the IVRS/IWRS at the baseline visit. Patients will access the IVRS weekly to record Pruritus numerical rating scale (NRS), per Section 6.3.3.6.

Details are provided in the study reference manual.

6.3.1.2. Physical Examination

A thorough and complete physical examination, including weight, height, will be performed at time points according to Section 6.2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.2. Safety Procedures

6.3.2.1. Vital Signs

Sitting vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected predose at time points according to Section 6.2. Vital signs will be taken at 30 (+/-10) minutes post-injection at visit 2 during the in-clinic 30-minute post-injection observation.

6.3.2.2. Ophthalmological Examination

This exam will be performed for certain patients of interest, as decided by the sponsor medical monitor in consultation with the investigator, at select study centers that have access and can refer patients to an eye specialist, either a General ophthalmologist or a Cornea and External Eye Disease ('front-of-the-eye') subspecialty expert. Any baseline findings will be documented as part of the patient's medical history and/or physical exam, as appropriate. Any inflammatory ophthalmological condition that occurs post-baseline will be captured as an AE. Additional tests and assessments may be performed to help understand the AEs. The method and procedure for the exam are provided in the study reference manual.

6.3.2.3. Injection Site Reaction

Clinical staff may photograph the site and complete the ISR electronic case report form (eCRF), in the event a patient experiences a visible ISR. Instructions for taking the photograph are provided in the study reference manual.

6.3.2.4. Laboratory Testing

Hematology, chemistry and serum pregnancy samples will be analyzed by a central laboratory.

Blood samples for serum chemistry testing will be collected to measure overall patient health at screening. Total basophil and eosinophil counts are of particular interest in AD patients, due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Section 6.2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Low-density lipoprotein (LDL)
Carbon dioxide	AST	High-density lipoprotein (HDL)
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK[1]

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN; CPK isoenzymes will be measured when CPK >5X the ULN

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Other Laboratory Tests

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points according to Section 6.2.

Testing for HIV antibody will be performed at screening; however, HIV testing is not required at screening for patients with a negative HIV result in the parent study within 1 year prior to baseline. Testing for HBsAg, HBcAb, and hepatitis C antibody will be performed at screening but an individual test is not required if patients had a negative result for the respective test within 1 year prior to baseline.

Additional tests may be required to verify eligibility, or to clarify or help manage AEs. Any laboratory tests that are not specifically noted in the protocol require written approval from the medical monitor.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 7.2.5.

6.3.3. Efficacy Procedures

6.3.3.1. Investigator's Global Assessment

The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (very severe). The IGA score will be assessed at time points according to Section 6.2.

The IGA is provided in the study reference manual.

6.3.3.2. Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin 2001). Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, arms, and legs, and converted to a score of 0 to 6. The EASI will be collected at time points according to Section 6.2.

The EASI assessment tool is provided in the study reference manual.

6.3.3.3. Patient Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) with a scoring system of 0 to 28; a high score is indicative of a poor QOL. The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available, at time points according to Section 6.2.

The POEM is provided in the study reference manual.

6.3.3.4. Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL (Badia 1999). The format is a simple response to 10 items, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available, at time points according to Section 6.2.

The DLQI is provided in the study reference manual.

6.3.3.5. EQ-5D

The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D as a measure of health related QOL, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death"

and 1 represents "perfect health." The questionnaires will be administered only to the subset of patients who fluently speak the language for which a validated translation of the questionnaire is available, at time points according to Section 6.2.

The EQ-5D is provided in the study reference manual.

6.3.3.6. Pruritus Numerical Rating Scale

The Pruritus NRS is a simple assessment tool that patients will use to report the average intensity of their pruritus (itch), during a 1 week recall period. Patients will access the IVRS/IWRS weekly, preferably around the same time each week, and be asked the following question:

- For average itch intensity: "On a scale of 0 – 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch overall, which is on average, during the past week?"

Patients will be trained on using the IVRS/IWRS to record their Pruritus NRS score at the baseline visit, and visit 6, and will be queried by site staff for compliance at each scheduled (and any unscheduled) clinic visit. Patients will complete the rating scale weekly through the last study visit, according to Section 6.2.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected at time points listed in Section 6.2. Any unused serum samples collected for drug concentration measurements may be used to investigate unexpected AEs.

6.3.4.2. Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Section 6.2.

Patients who test positive for ADA at their last study visit (early termination or end of study) may, based on the benchmark ADA titer in effect at the time, be asked to return to the clinic to have additional ADA samples collected for analysis within 6 to 12 months after their last dose of study drug, and thereafter at intervals of approximately 3 to 6 months until their titers fall below the benchmark titer.

6.3.5. Research Testing

Per amendment 6, research samples, optional genomics sub-study, and biomarker testing assessments will no longer be collected.

Any samples left over may be used to investigate unexpected AEs. Residual samples will be stored for up to 15 years after the study closes for exploratory research purposes.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drug.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of the study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug must be reported to the sponsor (or designee) and entered into the electronic data capture (EDC) system within 24 hours of identification. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the IRB/EC all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn, must be reported as an SAE.

Adverse Events of Special Interest: AEs of special interest (AESIs) will be entered into the EDC system within 24 hours of identification. The site will also notify the Regeneron medical monitor of the AESIs within 24 hours of identification.

Adverse events of special interest in this study include:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

Additional AESIs for the sub-study using the new dupilumab drug product:

- Any serious or severe ISR or any ISR lasting longer than 24 hours.

Refer to the study reference manual for the procedures to be followed.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

7.3.2. Evaluation of Causality

The relationship of AEs to study drug is a clinical decision that will be made, based on all available information, by the investigator, who will answer the following question:

Is there a reasonable possibility that the AE was caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug (ie, a causal relationship cannot reasonably be ruled out)

The investigator will provide a comment on the SAE reporting form to explain the basis of the causality assessment for SAEs.

7.3.2.1 Causality Evaluation Factors

Factors to consider when determining the relationship of an AE to study drug are included below.

Not Related:

- Existence of a clear alternative explanation or nonplausibility (eg, the patient is struck by an automobile when there is no indication that the drug caused disorientation, or cancer diagnosed a few days after first drug administration)
- Due to external causes such as other treatment/s being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed (ie, negative re-challenge)
- Is not a known response to the study drug based upon preclinical data or prior clinical data

Related:

- Could not be explained by other treatment/s being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug is resumed (ie, positive re-challenge)
- Known to be a response to the study drug based upon preclinical data or prior clinical data
- Known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson Syndrome)

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an on-going basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/investigational product).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, and medication history for each patient.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

- The primary endpoint in the study is the incidence and rate (events per patient-year) of treatment-emergent adverse events (TEAEs) through the last study visit.

8.2.2. Secondary Endpoints

The secondary endpoints are:

- Key secondary endpoints
  - Incidence and rate (events per patient-year) of SAEs and AESIs
  - Proportion of patients with IGA = 0-1 at each visit
  - Proportion of patients with EASI-75 (≥75% reduction in EASI scores from baseline of the parent study) at each visit
- Other secondary endpoints:
  - Proportion of patients with low disease activity state (eg, IGA ≤2) at each visit
  - Change and percent change from baseline in EASI score at each visit
  - Proportion of patients with EASI-50 (≥50% reduction in EASI scores from baseline of the parent study) at each visit
  - Proportion of patients with EASI-90 (≥90% reduction in EASI scores from baseline of the parent study) at each visit
  - Change and percent change from baseline in Pruritus NRS
  - Proportion of patients with improvement (reduction) of Pruritus NRS ≥3 from baseline
  - Proportion of patients with improvement (reduction) of Pruritus NRS ≥4 from baseline
  - Proportion of patients requiring rescue treatment:
    - Overall
    - Systemic treatment
      - Systemic corticosteroids
      - Systemic immunosuppressive drugs

  - Phototherapy
- Number of days on topical medication (per patient-year)
- Proportion of patients using topical medications over various periods during the study
- Changes from baseline to prespecified time points through the end of the study:
  - DLQI
  - POEM
  - EQ-5D

8.2.3. Sub-Study Endpoints

Primary Endpoints

- Incidence of AESIs through the last study visit after switching to the new dupilumab drug product.

Secondary Endpoints

- Trough concentrations (C_{trough}) of functional dupilumab in serum before and after switching to the new dupilumab drug product
- Incidence of treatment-emergent ADA response in patients receiving the new dupilumab drug product

Exploratory Endpoints

- Proportion of patients with IGA = 0 or 1 before (at sub-study week 0a [sub-study baseline]) and after switching to new dupilumab drug product (at sub-study week 12a)
- Change and percent change from baseline in EASI score at each visit
- Change and percent change from baseline in Pruritus NRS

8.3. Pharmacokinetic Variables

The PK variables in the main study may include, but are not limited to, the following:

- C_{trough}
- $C_{trough,SS}$
- C_{last}
- T_{last}

For the sub-study, C_{trough} will be assessed.

8.4. Anti-Drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Preexisting immunoreactivity
- Treatment-emergent
- Persistently positive
- Transiently positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the main study and for the sub-study. The SAP may be revised during the study (including sub-study) to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Data collected through the implementation of new case report forms (CRFs) regarding the impact of the COVID-19 pandemic on the patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

Analysis variables are listed in Section 8.

9.1. Statistical Hypothesis

There is no statistical hypothesis in this open-label study.

9.2. Justification of Sample Size

No formal sample size or power calculations were performed for this study.

9.3. Analysis Sets

9.3.1. Safety Analysis Set

The safety analysis set (SAF) includes all patients who received any study drug; it is based on the treatment received (as treated). Efficacy, treatment compliance/administration, and all clinical safety variables will be analyzed using the SAF, as treated.

9.3.2. Pharmacokinetic Analysis Set

The PK population includes all treated patients who received any study drug and who had a qualified result for drug concentration at any time during the study.

9.3.3. Analysis Set for Anti-Drug Antibody Data

The ADA population includes all treated patients who received any study drug and had at least 1 qualified result at any time during the study.

9.4. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

9.5. Statistical Methods

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

9.5.2. Safety Analysis

Safety analysis will be based on the SAF. A summary of safety results will be presented.

9.5.2.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as day 1 (from start of administration of the first dose of study drug) to end of study.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a preexisting condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized.

9.5.2.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.5.2.3. Treatment Exposure

The duration of exposure during the study will be presented and calculated as:

QW dosing: (Date of last study drug injection – date of first study drug injection) + 7 days, Q2W dosing: (Date of last study drug injection – date of first study drug injection) + 14 days.

The number (%) of patients exposed to study drug will be presented by specific time periods. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized using number of patients, means, standard deviation, minimums, medians, and maximums.

A summary of the number of doses will be provided.

9.5.2.4. Treatment Compliance

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment Compliance =

(Number of investigational product injections during exposure period)/(Number of planned investigational product injections during exposure period) x 100%

The treatment compliance will be presented by specific ranges. The ranges of interest will be specified in the SAP.

9.5.3. Efficacy Analyses

Descriptive statistics of the efficacy endpoints will be summarized for this open-label study. These include the proportions for category endpoints and basic statistics of original, absolute, and percentage change from baseline for continuous endpoints.

All observed data will be used for analysis.

Subgroup analyses for key efficacy endpoints will be performed. The subgroup of interest and endpoints to be analyzed will be specified in the SAP.

9.5.4. Analysis of Drug Concentration Data

The following analyses may be conducted:

- Sparse sampling:
  - Descriptive statistics at each sampling time
  - Mixed model analysis of variance of steady-state trough concentrations to determine between- and within-subject variability, as well as least square means

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 8.4 will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of the impact of ADA on safety and efficacy may be provided.

9.5.6. Analysis of the Sub-Study

Demographic and baseline characteristics will be summarized descriptively. Safety analyses will be conducted in descriptive fashion as described in Section 9.5.2.1 and Section 9.5.2.2. Efficacy analyses will be conducted in descriptive fashion as described in Section 9.5.3. Treatment compliance and treatment exposure will be analyzed in a similar fashion as described in Section 9.5.2.3 and Section 9.5.2.4.

Under Amendment 10, a primary analysis of the sub-study is planned once all patients who enter the sub-study complete 12 weeks of the new dupilumab drug product treatment period (sub-study week 12a visit or earlier for those patients who are withdrawn prematurely from the study).

9.5.6.1. Statistical Hypothesis for the Sub-Study

There is no statistical hypothesis for the sub-study.

9.5.6.2. Justification of the Sub-Study Sample Size

No formal sample size or power calculations were performed for the sub-study.

9.5.6.3. Analysis Sets for the Sub-Study

Safety Analysis Set:

The sub-study SAF includes all patients who receive any new dupilumab drug product in the sub-study. Efficacy, treatment compliance/administration, and all clinical safety variables will be analyzed using the SAF, as treated.

Pharmacokinetic Analysis Sets:

The sub-study PK population includes all treated patients who enter the sub-study (implemented under amendment 10), who receive any new dupilumab drug product, and who have a qualified result for drug concentration at any time during the sub-study period.

Anti-Drug Antibody Analysis Set

The sub-study ADA population includes all treated patients who receive any new dupilumab drug product and have at least 1 qualified result at any time during the sub-study period after the first dose of new dupilumab drug product. All ADA analysis will be conducted using this population.

9.5.6.4. Statistical Methods for Sub-Study

Safety Analysis:

Summaries of AESIs will include:

- Treatment-emergent AESIs presented by AESI category, high-level term, and PT
- The number (n) and proportion (%) of patients with at least 1 treatment-emergent AESI by AESI category, high-level term, and PT
- Exposure-adjusted treatment-emergent AESIs presented by AESI category, high-level term, and PT

Summaries of all TEAEs will include:

- The number (n) and proportion (%) of patients with at least 1 TEAE by SOC and PT
- The number (n) and proportion (%) of patients with at least 1 SAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation presented by SOC and PT

Deaths and other SAEs will be listed and summarized.

Treatment-emergent adverse events occurring before and after switching to the new dupilumab drug product will be summarized and listed separately using the SAF of the sub-study.

PK Analysis:

Trough concentrations of dupilumab will be summarized using descriptive statistics at each sampling time point including n, mean, median, standard deviation, geometric mean (as appropriate), coefficient of variation (if appropriate), and minimum and maximum values.

ADA Analysis:

Listings of ADA positivity, treatment-emergent ADA, and titers presented by patient and time point will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%) grouped by ADA titer level. The ADA variables will be summarized and listed by before (sub-study week 0a) and after switching to the new dupilumab drug product using the SAF of the sub-study. Additional details of ADA data analysis for the sub-study will be provided in the SAP.

Efficacy Analysis:

The efficacy endpoints will be summarized using descriptive statistics. These include the proportions for categorical endpoints and basic statistics of original, absolute, and percentage change from baseline for continuous endpoints.

All observed data will be used for analysis.

All efficacy endpoints will be summarized by before and after switching to the new dupilumab drug product using the SAF of the sub-study.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid predose assessment available.

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, electrocardiogram data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an EDC tool.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system –study drug supply, patient dosing and pruritus assessment
- EDC system – data capture
- Statistical Analysis Software (SAS) – statistical review and analysis
- PVRM Safety System

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study medication will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: AN OPEN-LABEL STUDY OF DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS WHO PARTICIPATED IN PREVIOUS DUPILUMAB CLINICAL TRIALS, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study and the data generated.

Study Title: An Open-Label Study of Dupilumab in Patients with Atopic Dermatitis who Participated in Previous Dupilumab Clinical Trials

Protocol Number: R668-AD-1225

Protocol Version: R668-AD-1225 Amendment 10

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00152209 v1.0

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