	• Change from baseline in Hospital Anxiety and Depression Scale (HADS) at all scheduled time points; • Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at all scheduled time points; • Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Change from baseline at all scheduled time points in SCORAD subjective assessments of itch and sleep loss; • Steroid-free days at Week 16.
Safety Objectives	**Safety Endpoints**
To compare the safety and tolerability of 100 mg and 200 mg QD of PF-04965842 and dupilumab versus placebo in adult subjects on background topical therapy with moderate to severe AD. To estimate the safety and tolerability of the two doses of PF-04965842 versus dupilumab, for adult subjects on background topical therapy with moderate to severe AD.	• Incidence of treatment-emergent adverse event (AE)s; • Incidence of serious adverse event (SAE)s and AEs leading to discontinuation; • Incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs.

CCI [redacted]

willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Subjects for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion 3 and who subsequently experience worsening AD, which in the investigator's judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.

Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 4:4:4:1:1 ratio to receive 100 mg or 200 mg of PF-04965842 QD with dupilumab-matching placebo administered every other week , dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with PF-04965842-matching placebo administered QD, or one of two sequences of PF-04965842-matching placebo administered QD with dupilumab-matching placebo administered every other week from Day 1, for 16 weeks followed by either 100 mg or 200 mg of PF-04965842 QD. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

The total treatment period is 20 weeks. The first part of this treatment period consists of a 16-week randomized, double-blind, placebo-controlled, double-dummy treatment period with subjects receiving both injectable and oral investigational product. The randomization and double-blind will be maintained during the final 4 weeks of the treatment period, but subjects will only receive oral investigational product. At Week 16 in the treatment period, all subjects will cease injectable dupilumab or its matching placebo. This is to facilitate the washout of dupilumab (for a total of 6 weeks; as the final dose of dupilumab or its matching placebo is administered at Week 14) prior to eligible subjects entering the long-term extension study, in which all subjects will receive PF-04965842 active treatment. As, following Week 16, data for the primary and key secondary efficacy assessments will have already been obtained, subjects previously receiving only placebo will receive PF-04965842 100 mg or 200 mg QD as per their randomized allocation. Subjects previously receiving PF-04965842 100 mg or 200 mg QD will continue on their respective dose. Subjects previously receiving dupilumab will continue to take oral placebo. These alterations to study treatment will all be conducted while maintaining the blind when re-issuing oral investigational product to all subjects at the Week 16 time point.

Eligible subjects completing the entire 20-week treatment period of the study will have the option to enter a long-term extension (LTE) study, B7451015. In which all subjects will receive PF-04965842 active treatment. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study, will undergo a 4-week follow-up period in study B7451029.

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Provide Patient Emergency Contact Card	X										
Medical Procedures											
Complete Physical Exam[e]	X	X								X	X
Targeted Physical Exam[e]				X	X	X	X	X	X		
Vital Signs[f]	X	X		X	X	X	X	X	X	X	X
Weight	X	X					X			X	
Height	X										
Chest X-ray[g]	X										
ECG (12-lead)	X[h]	X		X	X	X	X	X	X	X	X
Laboratory Assessments											
Serum Chemistry and Hematology (including Coagulation Panel)[i]	X	X		X	X	X	X	X	X	X	X
Lipid Panel[i]		X			X			X		X	X
CCI [redacted]											
Urinalysis	X	X		X	X	X	X	X	X	X	X
Serum FSH (WONCBP only) or Pregnancy Test[l]	X										
Urine Pregnancy Test (conducted at study site)[m]		X		X	X	X	X	X	X	X	X
CCI [redacted]											
HIV Testing[o]	X										

Table 1. Objectives and Endpoints:

Primary Objective	Primary Endpoints
To compare the efficacy of 100 mg and 200 mg once daily (QD) of PF-04965842 versus placebo in adult subjects on background topical therapy with moderate to severe atopic dermatitis (AD).	The following co-primary endpoints will be tested: • Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day 1) of ≥2 points at Week 12; • Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 12.
Secondary Objectives	**Secondary Endpoints**
To compare the efficacy of PF-04965842 versus dupilumab in terms of attaining a clinically significant improvement in the severity of pruritus for adult subjects on background topical therapy with moderate to severe AD.	**Key Secondary Endpoints:** • Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at Week 2.
To estimate the difference in efficacy measures between two doses of PF-04965842 and dupilumab for adult subjects on background topical therapy with moderate to severe AD.	• Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16; • Response based on achieving EASI-75 (≥75% improvement from baseline) at Week 16.
To estimate the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in adult subjects on background topical therapy with moderate to severe AD.	**Secondary Efficacy Endpoints:** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and ≥2 point reduction from baseline at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥75% improvement in the EASI total score (EASI-75) at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥50%, ≥90%, and 100% improvement in the EASI total score (EASI-50, EASI-90, and EASI-100) at all scheduled time points; • Response based on achieving at least 4 points improvement in the severity of Pruritus NRS from baseline at all scheduled time points except Week 2; • Time from baseline to achieve at least 4 points improvement in the severity of Pruritus NRS scale; • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; • Change from baseline of Patient Global Assessment (PtGA) at all scheduled time points; • Change from baseline in Dermatology Life Quality Index (DLQI) at all scheduled time points; • Change from baseline in EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) at all scheduled time points;

6.4. Subject Withdrawal

Ongoing safety concern at the time of subject withdrawal from the study:

If a subject has a clinically significant, treatment-emergent, abnormality at the time of withdrawal from the study, the Pfizer Medical Monitor (or designee) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormality. All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels or are deemed clinically stable. Follow-up for abnormal laboratory findings and adverse events by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Appendix 4 for Guidelines for Monitoring and Discontinuation.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study. If this request occurs at a scheduled visit, an end of treatment visit should be performed and the subject should enter into the follow-up period, with an end of study visit scheduled for 4 weeks after the end of treatment visit. If the request occurs outside of a scheduled visit (eg, via telephone contact) the subject should be scheduled to return to site for an end of treatment visit within one week, and the subject should enter into the follow-up period, with an end of study visit scheduled for 4 weeks after the end of treatment visit.

The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to

7.1. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed at screening. A urine pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed at every site visit including the End of Treatment (EOT) and follow-up visits to confirm the subject has not become pregnant during the study, and at the follow-up visit.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study.

CCI

visit. Weight (lb or kg) will continue to be measured and recorded at various time points, see Schedules of Activities.

Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Complete physical examinations consist of assessments of general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth, heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; and lymph nodes.

Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject.

Complete and Targeted physical examinations are performed at various time points, see Schedules of Activities.

7.3.3. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) with no evidence of current, active TB or previous inactive TB, taken at screening or within 12 weeks prior to Study Day 1 and read by a qualified radiologist, are required. Documentation of the official reading must be located and available in the source documentation.

7.3.4. Tuberculosis Testing

At the time of screening, all subjects will undergo tuberculosis (TB) testing unless performed within 12 weeks of Day 1. QuantiFERON®-TB Gold In-Tube Test is the preferred testing method. If the test results are indeterminate, the test should be repeated. If the QuantiFERON®-TB Gold In-Tube test cannot be performed, or if the results of the repeat test are indeterminate, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Skin Test (Mantoux method) with approval of the Pfizer Medical Monitor.

In addition to TB testing as specified in this clinical protocol, a chest X-ray will be performed to aid in TB status determination.

QuantiFERON®-TB Gold In-Tube is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-gamma by Enzyme-Linked Immunosorbent Assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QuantiFERON®-TB Gold In-Tube is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

7.6.2. Laboratory Tests

The following laboratory tests will be performed at time points identified in the Schedule of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

Sample collection, labeling, storage, and shipping information can be found in the laboratory manual. All laboratory tests with clinically important changes from baseline identified after administration of investigational product will be followed until the value stabilizes.

Subjects must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel on Day 1, Week 4, Week 16, Week 20 and EOS. For all other lab tests, fasting is not required.

7.8.2. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment of atopic dermatitis is scored on a 5-point scale (0-4), reflecting a global consideration of the erythema, induration and scaling. The clinical evaluator of atopic dermatitis will perform an assessment of the overall severity of atopic dermatitis and assign an IGA score and category as described in Table 2. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 2. Investigator's Global Assessment (IGA) Score

Score	Category	Description*
0	Clear	Atopic dermatitis is cleared, except for any residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Almost Clear	Overall, the atopic dermatitis is not entirely cleared and remaining lesions are light pink (not including post inflammatory hyperpigmentation) and/or; have barely palpable hard thickened skin and/or papules and/or; have barely perceptible lichenification; excoriation and oozing/crusting are absent.
2	Mild	Overall, the atopic dermatitis consists of lesions that are light red; with slight, but definite hard thickened skin and/or papules; with slight, but definite linear or picked scratch marks or penetrating surface injury; with slight, but definite thickened skin, fine skin markings, and lichenoid scale; oozing/crusting is absent.
3	Moderate	Overall, the atopic dermatitis consists of lesions that are red; with easily palpable moderate hard thickened skin and/or papules; with moderate linear or picked scratch marks or penetrating surface injury; with moderate thickened skin, coarse skin markings, and coarse lichenoid scale; with slight oozing/crusting.
4	Severe	Overall, the atopic dermatitis consists of lesions that are deep, dark red; with severe hard thickened skin and/or papules; with severe linear or picked scratch marks or penetrating surface injury; with severe thickened skin with very coarse skin markings and lichenoid scale; with moderate to severe oozing/crusting.

* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

7.8.3. SCORAD

SCORAD is a validated scoring index for atopic dermatitis, which combines extent (0-100), severity (0-18), and subjective symptoms (0-20) based on pruritus and sleep loss, each scored using a visual analog scale (0-10).

Extent (A, maximum score of 100%)

To determine extent of AD, rule of 9 is used to calculate body surface area affected by AD as a percentage of the whole body surface area. Body surface area as percentage of total body surface area for each body region is as follows:

- Head and neck 9%;
- Upper limbs 9% each;
- Lower limbs 18% each;

Frequency of Pruritus

The frequency of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess frequency of itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms "never/no itching" (0) and "always/constant itching" (10). Subjects will enter Pruritus NRS assessment into an eDiary. Frequency of pruritus will not be included in the evaluation of Inclusion Criteria 3 (See Section 4.1).

The Pruritus NRS should be completed as per Schedule of Activities.

CCI

[redacted]

7.10.3. Patient Global Assessment (PtGA)

The PtGA asks the subject to evaluate the overall cutaneous disease at that point in time on a single-item, 5-point scale (Appendix 8). The same category labels used in the Investigator's Global Assessment will be used for the Patient Global Assessment, ie, "severe (4)", "moderate (3)", "mild (2)", "almost clear (1)", and "clear (0)". The PtGA should be completed as per Schedule of Activities.

7.10.4. EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L)

The EQ-5D is a validated, standardized, generic instrument that is the most widely used preference-based health-related quality of life questionnaire in cost-effectiveness and health technologies assessment (HTA) (Appendix 9).[21-24] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the EQ-5D-3L.[21,23,24-27]

CCI

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely 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 recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **Or** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications),

Additional secondary analyses will utilize missing at random (MAR) and missing not at random (MNAR) approaches. Missing observations will be multiply imputed using a tipping point analysis to estimate the treatment effect under the assumption that the missing data mechanism is MAR or more generally, is MNAR. A longitudinal logit-normal mixed model will be fit using only the observed data. Under the MAR framework, imputations will be based on the posterior predictive probability of response obtained from the posterior distribution under the mixed model. Under an MNAR framework, imputations for the active treatment groups will be based on a linear combination of the posterior predictive probability of response for the active group and the placebo group. For each such completed dataset, the estimates of the proportions and Cochran-Mantel-Haenszel (CMH)-weighted difference of proportions between each active dose group and placebo will be obtained and Rubin's rule will be used to combine the multiple estimates and standard errors across the imputed datasets and provide p-values.

9.2.4. Analysis of Secondary Endpoints

The key secondary endpoints which are summarized as proportions such as EASI-75, and the proportion of subjects achieving a 4-point improvement from baseline in the severity of Pruritus NRS measure will be analyzed using the same method as for the co-primary endpoints. This would also apply to any other binary endpoint in the study, such as the response based on subjects reported with PtGA of AD of clear (0) or almost clear (1) and ≥2 point improvement from baseline over 12 weeks.

For continuous endpoints, and change from baseline in the pruritus severity using the NRS measure at all scheduled time points, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, disease severity group, visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, Week 12, as well as at the other time points by time point-specific contrasts from the MMRM model.

9.3. Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards. All subjects who receive investigational product (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials;

- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles);
- Vital signs;
- ECG parameters if applicable.

Change from baseline on laboratory data and vital signs will be additionally summarized.

9.4. External Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Composition of the E-DMC and processes under which the E-DMC operates will be documented in the E-DMC charter.

9.5. Safety Adjudication Committees

To help assess the specific, complex safety events related to malignancies, cardiovascular events, and opportunistic infection (including eczema herpeticum and other infections of special interest) in this study, Safety Adjudication Committees, consisting of clinical experts in each of the relevant clinical areas, will be set up to harmonize and standardize assessments. In order to allow for an unbiased safety assessment, the members of these committees will be blinded to treatment assignment. Further information about the Safety Adjudication Committees can be found in their respective charters, including a specific description of the scope of their responsibilities, a plan where communication timelines are defined, and the exact process and definitions used by each committee to adjudicate the safety events that they will adjudicate. Other safety events for adjudication may be identified and included in the remit of the Safety Adjudication Committees as appropriate.

9.6. Week 16 Analysis and End of Study Analysis

There will be a total of two planned analyses conducted for the study. The Week 16 Analysis will be performed after the last subject in the study has the opportunity to complete the Week 16 visit. The Week 16 Analysis will constitute as the final analysis for the co-primary and key secondary endpoints, and the overall family-wise Type 1 error will be controlled as specified in Section 9.2.2. The conclusions with regards to the co-primary endpoints and the secondary endpoints will be based on this analysis, and hence the overall family-wise Type 1 error for this study is maintained. The results from the Week 16 Analysis will not be used to make decisions for modifying the study design or for stopping the study. Access to the database containing individual treatment group assignments will be restricted to the sponsor study team at the time of Week 16 Analysis. Study sites, investigators and subjects will not be unblinded.

Abbreviation	Term
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
e-Diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
EQ-5D-5L	EuroQol Quality of Life 5-Dimension 5-Level Scale
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
HADS	Hospital Anxiety and Depression Scale
HADS	Hospital Anxiety and Depression Scale
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
CCI [redacted]	[redacted]
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HCV RNA	hepatitis C viral ribonucleic acid
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
CCI [redacted]	[redacted]
HSV	herpes simplex virus

Appendix 12. Hospital Anxiety and Depression Scale (HADS)

HOSPITAL ANXIETY AND DEPRESSION SCALE: (Page 1 of 2)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **check the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed next to the replies.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought out-response.

1. I feel tense or 'wound up'
- ☐ 3 Most of the time
- ☐ 2 A lot of the time
- ☐ 1 From time to time, occasionally
- ☐ 0 Not at all

2. I still enjoy the things I used to enjoy
- ☐ 0 Definitely as much
- ☐ 1 Not quite so much
- ☐ 2 Only a little
- ☐ 3 Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen
- ☐ 3 Very definitely and quite badly
- ☐ 2 Yes but not too badly
- ☐ 1 A little, but it doesn't worry me
- ☐ 0 Not at all

4. I can laugh and see the funny side of things
- ☐ 0 As much as I always could
- ☐ 1 Not quite so much now
- ☐ 2 Definitely not so much now
- ☐ 3 Not at all

5. Worrying thoughts go through my mind
- ☐ 3 A great deal of the time
- ☐ 2 A lot of the time
- ☐ 1 Not too often
- ☐ 0 Very little

6. I feel cheerful
- ☐ 3 Never
- ☐ 2 Not often
- ☐ 1 Sometimes
- ☐ 0 Most of the time

7. I can sit at ease and feel relaxed
- ☐ 0 Definitely
- ☐ 1 Usually
- ☐ 2 Not often
- ☐ 3 Not at all

8. I feel as if I am slowed down
- ☐ 3 Nearly all of the time
- ☐ 2 Very often
- ☐ 1 Sometimes
- ☐ 0 Not at all

ECONOMIC ASSESSMENT – Healthcare Resource Utilization – Atopic Dermatitis (Page 2 of 2)

2) In last 3 months, have you been hospitalized due to Atopic Dermatitis? ☐ No ☐ Yes

If Yes, how many times?

_ _ _ _ hospitalizations

3) In last 3 months, have you visited the emergency room due to Atopic Dermatitis? ☐ No ☐ Yes

If Yes, how many times?

_ _ _ _ ER visits

4) In last 3 months, have you received any **physical treatments**, such as physical therapy/massage, acupressure/acupuncture, or chiropractic care to manage your **Atopic Dermatitis**? ☐ No ☐ Yes

If Yes, please estimate, how much money you have spent **out-of-pocket** on **physical treatments** to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

5) In last 3 months, have you used any **supplements (for example herbs, vitamins or other supplements)** to manage your **Atopic Dermatitis**? ☐ No ☐ Yes

If Yes, please estimate how much money you have spent **out-of-pocket** on these supplements to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

6) In last 3 months, please estimate how much money you have spent **out-of-pocket** on **all prescription medications** to manage your **Atopic Dermatitis**?

_ _ _ _ _ _ . _ _ _____

Does **copay** influence your decision regarding choice of treatment for your **Atopic Dermatitis**? ☐ No ☐ Yes

7) In last 3 months, please estimate how much money you spent **out-of-pocket** on **non-prescription (over-the-counter)** medications to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

8) In last 3 months, please estimate how much money you spent **out-of-pocket** on **professional services** to help with child care, housework, yard work or other activities of daily living that you cannot perform yourself due to your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

9) In last 3 months, how much time have other people spent **without receiving payment** to help you with child care, housework, yard work or other activities of daily living that you cannot perform yourself due to your **Atopic Dermatitis**?

_ _ _ _ hours

Appendix 17. Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 5.6) for the list of sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

AD = Atopic dermatitis; AE = Adverse Event; BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = Electrocardiogram; EQ-5D-5L = EuroQol Quality of Life 5-Dimension 5-Level Scale; HADS = Hospital Anxiety and Depression Scale; CCI
IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA = Patient Global Assessment; SAE = Serious Adverse Event; SCORAD = Scoring Atopic Dermatitis; CCI .

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Male or female subjects aged 18 years or older at the time of informed consent.

3. Meet all the following atopic dermatitis criteria:

   - Clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed atopic dermatitis at the screening and baseline visits according to Hanifin and Rajka criteria for AD[17] (see Appendix 2).

   - Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 weeks, or who have required systemic therapies for control of their disease.

     NOTE: Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescribed product).

   - Moderate to severe AD (affected body surface area (BSA) ≥10%, IGA ≥3, EASI ≥16, and Pruritus NRS severity score ≥4 on the day of the baseline visit).

4. During the last 7 days prior to Day 1, for the treatment of AD, the subject must have used only non-medicated topical therapy (ie, emollient) without other active ingredients indicated to treat AD, or other additives which could affect AD (eg, hyaluronic acid, urea, ceramide or filaggrin degradation products) at least twice daily, with response to treatment remaining inadequate at baseline. The subject must also be willing and able to comply with standardized background topical therapy, as per protocol guidelines (Section 5.9.1), throughout the remainder of the study.

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis B Core Antibody (HBcAb), Hepatitis C Antibody (HCVAb), Hepatitis C Viral RNA (HCV RNA)[p]	X										
HBV DNA testing for China, Japan, Republic of Korea, and Taiwan only[aa]	X						X			X	
Tuberculosis Test[q]	X										
Trial Treatment											
Randomization		X									
Oral Drug Dispensing		X			X	X	X	X			
Injectable Drug Dispensing		X		X	X	X	X				
Investigational Product Accountability				X	X	X	X	X	X	X	
Subject Injection Training[r]		X									
Observed Investigational Product Administration[s]		X		X	X	X	X	X	X	X	
Reallocation to new treatment regimens								X			
Review eDiary to assess completion		X	X	X	X	X	X	X	X	X	
Assess eligibility for B7451015[t]										X	
Clinical Assessments											
Fitzpatrick Skin Type Assessment		X									
Investigator's Global Assessment (IGA)	X	X		X	X	X	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X	X	X	X	X	X	X

complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. Subjects that discontinue study treatment will remain in the study and must have their end of treatment visit within 1 week after their last dose, and will then enter the 4-week follow-up period. See Appendix 4 for Guidelines for Monitoring and Discontinuation.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

CCI

[redacted]

A blood sample (approximately 3 mL) will be collected at screening for QuantiFERON®-TB Gold In-Tube testing. Following sample processing, the sample will be shipped to the sponsor's designated reference laboratory for testing. The procedure for processing and preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

A negative PPD test can be substituted for the QuantiFERON®-TB Gold In-Tube test only if the central laboratory is unable to perform the QuantiFERON®-TB Gold In-Tube test or cannot determine the results to be positive or negative and the Pfizer Medical Monitor approves it, on a case-by-case basis.

Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is also acceptable as the screening TB test. Like QuantiFERON®, the T-SPOT®.*TB* test is an in vitro diagnostic test for *M. tuberculosis* infection; however, it differs in that it uses a peptide cocktail of ESAT-6 and CFP-10 proteins to stimulate peripheral blood mononuclear cells.

T-SPOT®.*TB* testing will be performed at the site's local laboratory. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the T-SPOT®.*TB* test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval.

Purified Protein Derivative (PPD) Test

If the QuantiFERON®-TB Gold In-Tube test or the T-SPOT®.*TB* test (Japan only) cannot be performed, or if the results cannot be determined to be positive or negative, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Test (Mantoux method), with the approval of the Pfizer Medical Monitor.

Subjects must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test should be performed according to local standards with induration of <5 mm required for inclusion.

7.3.5. Electrocardiogram

A single 12-lead ECG will be performed at screening and all other on-site visits as specified in the Schedule of Activities. ECGs reading will be interpreted by a central reader.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

A subject's screening ECG must not demonstrate clinically significant abnormalities prior to randomization.

Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine	pH	HIV[a]
Hematocrit	Creatine Phosphokinase	Glucose (qual)	HBsAg[a]
RBC count and indices (MCH, MCHC, MCV,	Glucose	Protein (qual)	HBcAb[a]
	Na+, K+, Cl-, Ca++, P	Blood (qual)	HBsAb[b]
RBC	Total CO2 (Bicarbonate)	Ketones	HCVAb[a]
Morphology)	AST, ALT	Nitrites	HCV RNA[b]
Reticulocyte count	GGT	Leukocyte esterase	Serum FSH (WONCBP only) or
Platelet count	Total, Indirect & Direct	Microscopy and/or	Pregnancy Test[a, c]
WBC count with	Bilirubin	culture[d]	Urine pregnancy test[c]
differential	Alkaline phosphatase		QFT-G or PPD (if applicable) or
Total neutrophils (%, Abs)	Lactate dehydrogenase		T-SPOT®.*TB* test (Japan only)[e]
Eosinophils (%, Abs)	Uric acid		Viral Screen (if applicable)
Monocytes (%, Abs)	Albumin		[redacted] CCI
Basophils (%, Abs)	Total protein		
Lymphocytes (%, Abs)	Lipid Profile Panel[f]		
Coagulation Panel	Total cholesterol		
Activated Partial Thromboplastin Time (APTT)	LDL		
	HDL		
	Triglycerides		
Prothrombin Time/International Normalized Ratio (PT/INR)			HBV DNA

a. At Screening only. HIV testing will be performed for all subjects. Subjects who are positive for HIV will be screen-failed.

b. HBsAb reflex testing only if HBsAg negative but HBcAb positive. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. HCV RNA is reflex testing only if HCVAb is positive. Subjects who are positive for HCVAb and HCV RNA will be screen-failed.

c. Pregnancy testing for females of childbearing potential; serum FSH for postmenopausal female subjects who have been amenorrheic for at least 12 consecutive months.

d. Microscopy with culture performed as appropriate.

e. PPD results should be read within 48 to 72 hours. For Japan only: QFT-G is preferred but T-SPOT®.*TB* test may be performed instead through the site's local laboratory.

f. Lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 4, Week 16, Week 20, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides.

C [redacted]

h. For China, Republic of Korea and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for Hepatitis B Virus (HBV) DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner. For Japan only: Subjects with negative results for HBsAg, HBcAb and HBsAb tests may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner.

- Anterior trunk 18%;
- Back 18%;
- 1% for genitals.

The score for each body region is added up to determine the BSA affected by AD (A), which has a possible maximum score of 100%.

Severity (B, maximum score of 18)

A representative area of AD is selected. In this area, the severity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Erythema (reddening);
- Edema (swelling)/papulation;
- Oozing/crusting;
- Excoriation (scratch marks);
- Skin thickening (lichenification);
- Xerosis (dryness) (this is assessed in an area where there is no inflammation).

The severity scores are added together to give 'B' (maximum score of 18).

Subjective Symptoms (C, maximum score of 20)

Subjective symptoms, ie, itch and sleep loss, are each scored by the subject or caregiver using a visual analog scale (VAS) where "0" is no itch (or no sleep loss) and "10" is the worst imaginable itch (or sleep loss). The value for each should reflect the average on a 10 point scale for the last 3 days/nights. These scores are added to give 'C' (maximum score of 20).

SCORAD Total Score

The SCORAD for an individual is calculated by the formula: A/5 + 7B/2 + C (can range from 0 to 103).

7.8.4. Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a subject's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3-level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known-groups validity.[22,23,25,26] Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well-established instruments used to measure health states and utilities in various diseases areas and assess mobility, self-care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS.[24,28] The EQ-5D-3L was used previously in AD studies, including the dupilumab trials, to measure utilities.[29-32]

7.10.5. Dermatology Life Quality Index (DLQI)

The DLQI is a validated general dermatology questionnaire that consists of 10 items to assess subject-reported health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (Appendix 10).[33] It has been extensively used in clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 3 to 5 point change from baseline.[34] The DLQI should be completed as per Schedule of Activities.

7.10.6. Patient-Oriented Eczema Measure (POEM)

The POEM is a validated 7-item PRO measure used to assess the impact of AD recalled over the past week (Appendix 11). This instrument is appropriate for use by subjects aged 12 and older.[35,36] The POEM should be completed as per Schedule of Activities.

7.10.7. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week[37] (Appendix 12). The instrument has been validated for use by adolescents aged 12 and older.[37] The HADS should be completed as per Schedule of Activities.

7.10.8. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

The PSAAD is a daily patient reported symptom diary. The preliminary version (Appendix 13) is a 15-item questionnaire that includes 11 items developed to measure symptoms of atopic dermatitis, capturing those identified by patients to be most important, based on a 24-hour recall. Analysis of the PSAAD will be based solely on these 11 items. CCI [redacted] The PSAAD is an electronic PRO that was developed through concept elicitation and cognitive debriefing in AD patients ages 12 to 67; CCI [redacted] All technical documents describing measurement properties of the PSAAD will be submitted as required to the Regulatory Agencies upon finalization. The PSAAD should be completed by subjects as per Schedule of Activities on an eDiary.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample).

recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective

The purpose of the Week 16 Analysis is to accelerate final reporting timeline. The final clinical study report (CSR) for the study will be based on the results from the Week 16 Analysis.

The End of Study Analysis will contain additional data after the final database release and the results will be reported in a supplemental CSR.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic and/or paper form

Abbreviation	Term
HTA	health technologies assessment
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG	immunoglobulin G
IIV	inter individual variability
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IWR	interactive web response
JAK	Janus kinase
JAK1	Janus kinase 1
CCI	[redacted]
LDL	low-density lipoprotein
LFT	liver function test
LLQ	lower limit of quantification
LSLV	last subject last visit
LTE	long-term extension
MAA	marketing authorisation application
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
MnB	meningitidis serogroup B
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NB-UVB	narrowband ultraviolet B light
OTC	over the counter

HOSPITAL ANXIETY AND DEPRESSION SCALE: (Page 2 of 2)

9. I get a sort of frightened feeling like 'butterflies' in the stomach

- ☐ 0 Not at all
- ☐ 1 Occasionally
- ☐ 2 Quite often
- ☐ 3 Very often

10. I have lost interest in my appearance

- ☐ 3 Definitely
- ☐ 2 I don't take as much care as I should
- ☐ 1 I may not take quite as much care
- ☐ 0 I take just as much care as ever

11. I feel restless as if I have to be on the move

- ☐ 3 Very much indeed
- ☐ 2 Quite a lot
- ☐ 1 Not very much
- ☐ 0 Not at all

12. I look forward with enjoyment to things

- ☐ 0 As much as I ever did
- ☐ 1 Rather less than I used to
- ☐ 2 Definitely less than I used to
- ☐ 3 Hardly at all

13. I get sudden feelings of panic

- ☐ 3 Very often indeed
- ☐ 2 Quite often
- ☐ 1 Not very often
- ☐ 0 Not at all

14. I can enjoy a good book or radio or television program

- ☐ 0 Often
- ☐ 1 Sometimes
- ☐ 2 Not often
- ☐ 3 Very seldom

Now check that you have answered all the questions

Appendix 15. C SSRS - Columbia Suicide Severity Rating Scale

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT
dd - MMM - yyyy

Visit: _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING AND BASELINE VISIT (C-SSRS) - Page 1 of 3

☐ (1) NOT DONE Language administered: ☒ (44) English for USA

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal		Past ____ Months	
	Yes	No	Yes	No
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	☐	☐	☐	☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts about killing yourself?*** If yes, describe:	☐	☐	☐	☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	☐	☐	☐	☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	☐	☐	☐	☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	☐	☐	☐	☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

	Lifetime: Most Severe	Past ____ Months: Most Severe
Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in a week (4) Daily or almost daily (5) Many times each day	____	____

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 8.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.