NCT 03667014

Clinical Research Protocol

The impact of dupilumab on quality of life in moderate to severe atopic dermatitis patients

Protocol Number:	R668-AD-1833
Version Date:	February 14, 2019
Investigational Product:	Dupilumab
Sponsor:	Tina Bhutani, MD
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Funding Organization:	Regeneron Pharmaceuticals and Sanofi

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Regeneron with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: R668-AD-1833

Protocol Title: The impact of dupilumab on quality of life in moderate to severe atopic dermatitis patients

Protocol Date: February 14, 2019

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Investigator Signature *Date*

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Print Name and Title

Site Name _____

Address _____

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Phone Number _____

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Contents

LIST OF ABBREVIATIONS

AD	Atopic dermatitis
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CRF	Case Report Form
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EASI	Eczema area severity score
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IRB	Institutional Review Board
IUD	Intrauterine device
PGWB	Psychological General Well-Being scale
PI	Principal Investigator
PK	Pharmacokinetic
QoL	Quality of life
SAE	Serious adverse experience
WPAI	Work Productivity and Activity Impairment scale

PROTOCOL SYNOPSIS

TITLE	The impact of dupilumab on quality of life in moderate to severe atopic dermatitis patients
SPONSOR	Tina Bhutani, MD
FUNDING	Regeneron Pharmaceuticals and Sanofi
STUDY DESIGN & OVERVIEW	This is an open-label study which will examine the effect of dupilumab on quality of life in a real-world setting
PRIMARY OBJECTIVE	To evaluate the improvement in patient quality of life after 52 weeks of treatment with dupilumab using validated dermatologic and non-dermatologic psychometric instruments. The primary endpoint is the improvement in quality of life measured by change in Psychological General Well-Being scale (PGWB) at Week 16 from baseline.
SECONDARY OBJECTIVES	To evaluate physical parameters and patient reported symptoms and satisfaction with treatment after 52 weeks of dupilumab using validated dermatologic and non-dermatologic instruments.
NUMBER OF SUBJECTS	Up to 30 patients will be enrolled
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Ability to provide written informed consent and comply with the protocol 2. At least 18 years of age 3. Diagnosis of atopic dermatitis at least 6 months prior to enrollment, having stable (unchanged) disease for at least 2 months 4. Non-immune-compromised status 5. Subjects have moderate-to-severe atopic dermatitis, classified as Eczema Area and Severity Index (EASI) score greater than or equal to 6 6. Subject is considered a candidate for phototherapy or systemic therapy 7. Subjects of child-bearing potential must have a negative urine pregnancy test within 7 days prior to first dose of dupilumab 8. Sexually active subjects of childbearing potential must agree to use medically acceptable form of contraception during screening and throughout the study 9. Subject meets concomitant medication requirements (see below) Exclusion Criteria:

	1. Younger than 18 years of age 2. Has mild atopic dermatitis, classified as EASI score less than 6 3. History of known or suspected intolerance to any of the ingredients of the investigational study product 4. Evidence of skin conditions other than atopic dermatitis that would interfere with study-related evaluations of atopic dermatitis. 5. History of immune-compromised status [e.g. human immunodeficiency virus (HIV) positive status or other immune suppressing drug] or a congenital or acquired immunodeficiency 6. Has a poorly controlled medical condition including, but not limited to, unstable cardiovascular disease, poorly controlled diabetes, recent stroke, history of recurrent infections, or any other condition for which, in the opinion of the investigator, participation in the study would place the subject at risk 7. Has a history of or ongoing drug or alcohol abuse 8. Is not willing to comply with concomitant medication requirements 9. Is known, or suspected of being unable to comply with the study protocol 10. Subjects who are well controlled on current treatment for atopic dermatitis and participation in the study may worsen disease control significantly 11. Subjects who have been previously treated and/or are currently on dupilumab will not be eligible to participate.
STUDY TREATMENT	Dupilumab (Dupixent ®) 600 mg SC at week 0, then 300 mg SC every other week.
STUDY DURATION	The total duration of the study is expected to be 104 weeks: 52 weeks for recruitment and 52 weeks for site visits.
PRIMARY ENDPOINT	Improvement in quality of life measured by change in Psychological General Well-Being scale (PGWB) at Week 16 from baseline.
SECONDARY ENDPOINT	1. Improvement in work productivity measured by change in Work Productivity and Activity Impairment scale (WPAI) at Week 16 from baseline 2. Improvement in quality of life measured by change in Dermatology Life Quality Index (DLQI) at Week 16 from baseline 3. Efficacy of drug as measured by EASI and IGA at week 16 from baseline 4. Safety of drug 5. Improvement in itch and pain scores using numerical rating scales at Week 16 from baseline 6. Improvement in sleep quality measured by the Pittsburgh Sleep Quality Assessment (PSQI) at Week 16 from baseline

	7. Evaluation of subjective video documentation
SAFETY EVALUATIONS	Safety will be evaluated by tabulation of adverse events (AEs), including any Serious Adverse Events (SAEs) within treatment groups. All AEs occurring during the study will be recorded. Descriptions of adverse events will include the date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. All reported adverse events will be summarized by the number of subjects reporting adverse events, body system, severity, seriousness, and relationship to study treatment.
STATISTICS **Primary Analysis Plan**	The primary endpoint is improvement of PGWB at week 16 compared to baseline. Statistical significance will be based on resulting p-values of 0.05 or less. Last observation carried forward (LOCF) will be used to impute missing data. Analyses will be conducted on an intent-to-treat (ITT) population (all subjects enrolled and receiving the treatments). Analyses on the per-protocol (PP) population will be considered supportive of the ITT analyses. Subjects will be eligible for the PP analyses if they complete the 52 week evaluation without any noteworthy study protocol violations (i.e. failure to use the study medications or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).
ETHICAL CONSIDER-ATIONS	This study will be conducted in accordance with applicable laws and regulations and according to the recommendations of International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines and those of the Declaration of Helsinki (Edinburgh, 2000); only after approval for the study has been obtained from the relevant regulatory authority and relevant independent ethics committee (IEC). The institutional review board (IRB)/IEC must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. The subject must be consented using the approved ICF before any procedures specified in the protocol are performed.

1 BACKGROUND

Atopic dermatitis (AD) is a common, complex, immune-mediated condition affecting 5-15% of children and adults worldwide. Adults with AD suffer from severe pruritus and inflammatory skin rash with a chronic disease course.

Patients with moderate-to-severe AD report a multidimensional burden including itch, pain, sleep disturbance, anxiety and depression, and impaired health-related quality-of-life (HRQoL). Patients suffering from AD are more likely to be depressed when compared to the general population, which can lead to increased suicidal ideation. Furthermore, AD can create a negative impact in the workplace, as patients with the disease are more likely to miss work due to their skin symptoms. With the significant negative psychosocial impact of AD, patients not only want to improve their skin lesions, but also their personal experience with this chronic disease.

2 STUDY RATIONALE

The overall aim of this study is to demonstrate, beyond the Dermatology Life Quality Index (DLQI), improvement in the quality of life of adults with moderate-to-severe AD who are being treated with dupilumab for 1 year.

The University of California, San Francisco (UCSF) Skin Treatment Center is a high-volume atopic dermatitis referral center whose activities include outpatient care, a phototherapy unit, a Goeckerman tar treatment program, and over 20 clinical trials conducted over the past three years.

The Skin Treatment Center has conducted several similar studies in the treatment of moderate to severe plaque psoriasis, a disease which has taken more than 10 years to be seen as a respectable condition on par with other serious medical diagnoses. In the process of making psoriasis worthy of reimbursement from payers, the government, and even in the eyes of the general public, some key data attesting quantitatively the negative impact of the disease, played a very important role. Having been involved in this process, and learning from the psoriasis experience, our aim is to make atopic dermatitis as respectable as psoriasis, without spending upwards of 10 years to get to that point. The most critical data that can help AD attain this respected status is the quantitative documentation regarding the negative impact of the disease on patients that is comparable to other serious disorders. This cannot be done with the DLQI or any other skin specific instruments.

We have specifically chosen the Psychological General Well Being Index (PGWB) and Work Productivity and Activity Index (WPAI) as quality of life assessment tools because they are *not* specific to skin diseases; they have been used extensively for non-dermatologic serious medical conditions. By deliberately using validated QOL instruments applicable broadly to serious medical conditions, we hope to show that patients being considered for treatment have baseline deficiencies in psychological well-being and work productivity comparable to patients with

serious non-dermatological disorders (such has heart disease, cancer, and untreated diabetes). Moreover, we aim to go beyond this by involving a therapeutic intervention to hopefully show that treatment with dupilumab not only significantly improves these parameters, but also brings them to a level comparable to a disease-free non-patient population.

Beyond administering these questionnaires, we will also take a novel approach to assessing patient experience with a medication. Each patient will be given a video recording device to document their experience from a pre-dupilumab state to a post-dupilumab state in the privacy of their own home. Human-interest stories excite payers and the general public who are not healthcare providers. It is best to have both human-interest stories in a narrative form before and after treatment as well as quantitative documentation with the PGWB and WPAI.

It is hoped that the information gained from this study will not only provide more insight into the psychosocial and occupational impact of AD, but also confirm the value of dermatological care by demonstrating and documenting how an effective treatment modality like dupilumab can reverse these negative impacts.

Thus, in this real-world study of atopic dermatitis, we aim to examine the value and efficacy of medical intervention, extending beyond physical improvement, and into the realm of psychosocial and occupational functions.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the improvement in patient quality of life after 52 weeks of treatment with dupilumab using validated dermatologic and non-dermatologic psychometric instruments. The primary endpoint is the improvement in quality of life measured by change in Psychological General Well-Being scale (PGWB) at Week 16 from baseline.

3.2 Secondary Objectives

To evaluate physical parameters and patient reported symptoms and satisfaction with treatment after 52 weeks of dupilumab using validated dermatologic and non-dermatologic instruments.

4 STUDY DESIGN

4.1 Study Overview

This is a single-center study. Up to thirty subjects with moderate to severe atopic dermatitis will receive dupilumab for a treatment period of 52 weeks. Patients will be evaluated using validated dermatologic and non-dermatologic psychometric instruments throughout the study period to measure quality of life, as well as satisfaction and symptom measures. Additionally, patients will

record their experience with the study drug at home during the study period. See Appendix 1 for a timeline of study activities.

5 CRITERIA FOR EVALUATION

5.1 Primary Analysis Endpoint

Improvement in quality of life measured by change in Psychological General Well-Being scale (PGWB) at Week 16 from baseline.

5.2 Secondary Analysis Endpoints

1. Improvement in work productivity measured by change in Work Productivity and Activity Impairment scale (WPAI) at Week 16 from baseline
2. Improvement in quality of life measured by change in Dermatology Life Quality Index (DLQI) at Week 16 from baseline
3. Efficacy of drug as measured by EASI and IGA at week 16 from baseline
4. Safety of drug
5. Improvement in itch and pain scores using numerical rating scales at Week 16 from baseline
6. Improvement in sleep quality measured by the Pittsburgh Sleep Quality Assessment (PSQI) at Week 16 from baseline
7. Evaluation of subjective video documentation

5.3 Safety Evaluations

Safety and tolerability to dupilumab will be assessed by adverse events, vital signs, physical examinations (including skin examinations and injection-site evaluations), and concomitant medication review. Laboratory assessments will be performed at screening.

6 SUBJECT SELECTION

6.1 Study Population

Subjects will be selected from qualified volunteers at least 18 years of age, with stable (unchanged for 2 months), moderate to severe atopic dermatitis who are candidates for phototherapy or systemic therapy.

6.2 Inclusion Criteria

1. Ability to provide written informed consent and comply with the protocol
2. At least 18 years of age
3. Diagnosis of atopic dermatitis at least 6 months prior to enrollment, having stable (unchanged) disease for at least 2 months

4. Non-immune-compromised status
5. Subjects have moderate-to-severe atopic dermatitis, classified as Eczema Area and Severity Index (EASI) score greater than or equal to 6
6. Subject is considered a candidate for phototherapy or systemic therapy
7. Subjects of child-bearing potential must have a negative urine pregnancy test within 7 days prior to first dose of dupilumab
8. Sexually active subjects of childbearing potential must agree to use medically acceptable form of contraception during screening and throughout the study
9. Subject meets concomitant medication requirements as documented below

6.3 Exclusion Criteria

1. Younger than 18 years of age
2. Has mild atopic dermatitis, classified as EASI score less than 6
3. History of known or suspected intolerance to any of the ingredients of the investigational study product
4. Evidence of skin conditions other than atopic dermatitis that would interfere with study-related evaluations of atopic dermatitis
5. History of immune-compromised status [e.g. human immunodeficiency virus (HIV) positive status or other immune suppressing drug] or a congenital or acquired immunodeficiency
6. Has a poorly controlled medical condition including, but not limited to, unstable cardiovascular disease, poorly controlled diabetes, recent stroke, history of recurrent infections, or any other condition for which, in the opinion of the investigator, participation in the study would place the subject at risk
7. Has a history of or ongoing drug or alcohol abuse
8. Is not willing to comply with concomitant medication requirements
9. Is known, or suspected of being unable to comply with the study protocol
10. Subjects who are well controlled on current treatment for atopic dermatitis and participation in the study may worsen disease control significantly
11. Subjects who have been previously treated and/or are currently on dupilumab will not be eligible to participate.

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

As this is a real-world trial, during the course of the study, subjects may continue treatment with topical steroids, phototherapy, or other systemic agents as deemed appropriate by the study investigators.

Any medications that the subject receives during the study must be recorded. Vaccines administered to the subject should be listed as a concomitant medication.

7.2 Prohibited Medications and Treatments

During the study period, concurrent use of other biologic medications apart from the study medication is prohibited. No new treatments should be added during the study period that the patient was not using consistently prior to study onset.

8 STUDY TREATMENTS

8.1 Supply of Study Drug at the Site

Regeneron will ship the study drug to the investigational sites. The study drug is supplied in cartons containing either two 300 mg/2 mL solution pre-filled syringes with needle shield or 2 pre-filled syringes. Each kit of study drug will be labeled with the required FDA warning statement, the protocol number, and directions for use and storage.

8.2 Storage

Dupilumab must be refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. The medication will be kept in a temperature-monitored refrigerator at the study site. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. The product will be kept in the original carton until the time of use.

8.3 Dosage/Dosage Regimen

Dupilumab will be administered at an initial dose of 600 mg subcutaneously followed by 300 mg subcutaneously through the study, which is the FDA-approved and recommended dose for dupilumab. There is no weight-based dosing. The dosing schedule will be as follows: dupilumab 600mg subcutaneously once at week 0, followed by dupilumab 300 mg subcutaneously every other week until week 50.

8.4 Administration Instructions

Doses of study treatment will be administered at the study site after the study assessments for the visit have been completed, at visits occurring between weeks 0 and 48. Subjects will administer the medication independently every other week only after they have demonstrated the competency to self-administer the treatment outside of the study site. Patients not demonstrating competency to self-administer the treatment will be administered the medication at the study site as needed. There will be no study medication given after week 50 of the study.

The subject should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled. All dates and times of injections done to the subject during the study must be recorded on the Dosage Administration Record CRF. The investigator will promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study.

8.5 Study Drug Accountability

The qualified site personnel will maintain an accurate record of the shipment and dispensing of study treatment in a treatment accountability log. All study treatment kits assigned to the subject during the study will be recorded.

8.6 Measures of Treatment Compliance

Subjects will be given scheduled doses of dupilumab at each visit from visit 2 (week 0) until visit 14 (week 48). Subjects will be given a dosing diary at every visit between weeks 0 and 48 to record their scheduled injections administered at home every other week.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

All clinical assessments will take place at the study site at 515 Spruce St., San Francisco, CA 94118.

All blood draws will take place at UCSF Blood Draw Lab at Mount Zion at 2330 Post St., First Floor, San Francisco, CA 94115.

9.1 Clinical Assessments

9.1.01 Medical History

Relevant medical history, including history of current disease and previous atopic dermatitis treatment, and information regarding underlying diseases will be recorded at Screening.

9.1.02 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Screening, at every site visit, and at early termination when applicable. Dose, route, unit frequency of administration, indication for administration, and dates of medication will be captured.

9.1.03 Demographics

Demographic information (date of birth, age, gender, ethnicity) will be recorded at Screening.

9.1.04 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at Screening. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.05 Vital Signs

Body temperature, blood pressure, pulse, and respirations will be performed after resting for 5 minutes at all site visits. Height and weight will additionally be measured at each study visit.

9.1.06 Adverse Events

Information regarding occurrence of adverse events will be captured at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.1.07 EASI and IGA

Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA) will be completed at Screening and weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable.

9.1.08 Quality of life measures

Quality of life measures will be assessed at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable.

Quality of life measures will be assessed using the following validated instruments:

1) Psychological General Well-Being scale (PGWB)
2) Work Productivity and Activity Impairment scale (WPAI)
3) Dermatology Life Quality Index (DLQI)

9.1.09 Symptom and satisfaction measures

Symptom and satisfaction measures will be assessed at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable.

Symptom and satisfaction measures will be assessed using the following validated instruments:

1) Itch Numerical Rating Scale
2) Pain Numerical Rating Scale
3) Pittsburgh Sleep Quality Assessment (PSQI)

9.1.10 Photography

Photographs (full front and back, excluding the face) will be taken at weeks 0, 16, 24, 52, and at early termination when applicable.

9.1.11 Video recording

Patients will be given a video recording device at week 0, and will be instructed on how to use it to record video. Patients will be instructed to record videos of themselves at home discussing their experience with the study drug and its impact on their skin and quality of life for roughly 5-10 minutes/week. The patient will be the only person in the video (i.e. there will be no family members or others interviewing or participating in the video). The patient will be encouraged to

record in a private setting (i.e. alone in their bedroom or office) and similarly, will be instructed to keep the recording device and its stored footage in a private location. Patients will be given a list of topics at the week 0 visit to be used as guidelines for discussion:

1) Please discuss any changes you have observed in your skin while using the study drug.
2) What is the most important change that you have experienced while using the study drug?
3) What are your goals with undergoing this medication for the future?
4) Please discuss how these changes in your skin have impacted both your life (day-to-day behaviors such as clothing choice or activities) and the lives of your loved ones.
5) Please discuss any changes in how you feel since starting the study medication (mood, sleep, work, home life, personal relationships).
6) Please discuss your overall experience using the study drug.
7) Please discuss any interesting or notable experiences or events that have occurred to you while using the study drug.
8) Please feel free to discuss anything else pertaining to your experience with eczema

Patients will be instructed to bring in their video recording devices to their study visits at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable. At these visits, study staff will download the patient videos to a secure local storage site.

9.1 Clinical Laboratory Measurements

9.2.01 Hematology

Blood will be obtained and sent to the clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count) for determination of systemic evidence for infection and/or inflammation at Screening.

9.2.02 Blood Chemistry Profile

Blood will be obtained and sent to the clinical chemistry lab for determination of electrolyte levels, serum BUN, creatinine, AST, ALT, and alkaline phosphatase at Screening.

9.2.03 Pregnancy Test

A urine pregnancy test will be obtained at the study site for female subjects of childbearing potential at Screening and weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early termination when applicable.

10 EVALUATIONS BY VISIT

See Appendix 1 for Evaluation Schedule.

10.01 Visit 1 (Screening)

1. Verify that patient meets all inclusion criteria and exclusion criteria
2. Informed Consent/HIPAA Authorization/UCSF Experimental Subject's Bill of Rights - Prior to any testing under this protocol, including screening and evaluations, written

informed consent will be obtained from the subject by the investigators. The background of the proposed study, benefits, and risks of procedures will be explained to the subject. Informed consent will be obtained after the subject has a chance to ask questions. A copy of the signed and dated informed consent, HIPAA Authorization, and UCSF Experimental Subject's Bill of Rights will be given to the subject. At the time of written informed consent, subjects will be given the name and phone number of personnel at the study site that can be called in the event of an emergency or to report any medical symptoms or untoward medical occurrence that is of concern to the subject.

3. Obtain patient demographic information
4. Medical history – a full medical history including all medications
5. Atopic dermatitis treatment history – past treatments with special focus on any treatment during the last 30 days
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Comprehensive physical exam
    d. Eczema Area and Severity Index (EASI)
    e. Investigator's Global Assessment (IGA)
7. Clinical Laboratories:
    a. Hematology
    b. Chemistry
8. Urine Pregnancy Test (if applicable)

10.02 Visit 2 (Week 0)

1. Review inclusion and exclusion criteria
2. Brief interim medical history
3. Review concomitant medications
4. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
5. Urine pregnancy test (if applicable)
6. Full-body photography (excluding face)
7. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI

8. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
9. Study drug injection
10. Dispense study medication and dosing diaries for home use
11. Sign out video recording device and instruct patients on proper use

10.03 Visit 3 (Week 4)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.04 Visit 4 (Week 8)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications

4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.05 Visit 5 (Week 12)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI

9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.06 Visit 6 (Week 16)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Full-body photography (excluding face)
9. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
10. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
11. Study drug injection
12. Dispense study drug and dosing diary for home use

10.07 Visit 7 (Week 20)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications

4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.08 Visit 8 (Week 24)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Full-body photography (excluding face)
9. Quality of Life Measures:
    a. WPAI
    b. PGWB

c. DLQI

10. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
11. Study drug injection
12. Dispense study drug and dosing diary for home use

10.09 Visit 9 (Week 28)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.10 Visit 10 (Week 32)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications

4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.11 Visit 11 (Week 36)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI

9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.12 Visit 12 (Week 40)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.13 Visit 13 (Week 44)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos

5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)
10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.14 Visit 14 (Week 48)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
9. Other patient questionnaires:

a. Itch Numerical Rating Scale
b. Pain Numerical Rating Scale
c. Pittsburgh Sleep Quality Assessment (PSQI)

10. Study drug injection
11. Dispense study drug and dosing diary for home use

10.15 Visit 15 (Week 52)

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration
6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Full-body photography (excluding face)
9. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
10. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)

10.16 Early termination

1. Brief interim medical history
2. Review adverse events
3. Reconcile concomitant medications
4. Study staff download patient videos
5. Study staff collect, review, and record home study drugs administration

6. Physical examination
    a. Height and weight
    b. Vital signs: temperature, blood pressure, pulse, and respiratory rate
    c. Eczema Area and Severity Index (EASI)
    d. Investigator's Global Assessment (IGA)
7. Urine pregnancy test (if applicable)
8. Full-body photography (excluding face)
9. Quality of Life Measures:
    a. WPAI
    b. PGWB
    c. DLQI
10. Other patient questionnaires:
    a. Itch Numerical Rating Scale
    b. Pain Numerical Rating Scale
    c. Pittsburgh Sleep Quality Assessment (PSQI)

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in **Error! Reference source not found.** below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.

Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

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

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is otherwise a significant medical event.

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness(es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

11.3. Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

Timelines: All serious adverse events (SAEs) must be reported by the sites to Sponsor within 24 hours of occurrence of the SAE. The timelines for investigator initiated trials reporting to Regeneron Pharmaceuticals will be done as per Third Party Study/Investigator Initiated Trial Agreement. All reports must be sent to Regeneron as below:

- Fax SAE/CIOMS or MedWatch Reports to 914-345-7476
- Email forms to medical.safety@regeneron.com

Follow-up reports: SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Sponsor shall support Regeneron in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Regeneron to any Health authority OR specific Health authority follow-up requests for the product under investigation.

Pregnancies: Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as

soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10.13 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 11) should have an early discontinuation visit. Refer to Section 10.13 for early termination procedures. Subjects who withdraw after Visit 1 but prior to Visit 10 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit). Subjects who sign the informed consent form (ICF) and who are discontinued or withdraw from the study before study product administration will be defined as screen failures. No data will be collected in the CRFs for screen failure subjects.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria.
- Use of a prohibited concomitant medication.
- Non-compliance with study drug regimen.
- Non-compliance with study visit procedures.
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory

binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Analysis of Primary Endpoint

The primary endpoint is improvement of PGWB at week 16 compared to baseline. Statistical significance will be based on resulting p-values of 0.05 or less. Last observation carried forward (LOCF) will be used to impute missing data. Analyses will be conducted on an intent-to-treat (ITT) population (all subjects enrolled and receiving the treatments). Analyses on the per-protocol (PP) population will be considered supportive of the ITT analyses. Subjects will be eligible for the PP analyses if they complete the 52 week evaluation without any noteworthy study protocol violations (i.e. failure to use the study medications or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).

14.2 Analysis of Secondary Endpoints

1. **Efficacy Endpoints**
    - **a.** EASI and IGA scores at week 16 will be compared to baseline.
2. **Safety Endpoints**
    - **a.** Safety will be evaluated by tabulation of adverse events (AEs), including any Serious Adverse Events (SAEs) within treatment groups. All AEs occurring during the study will be recorded. Descriptions of adverse events will include the date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. All reported adverse events will be summarized by the number of subjects reporting adverse events, body system, severity, seriousness, and relationship to study treatment.
3. **Analysis of Other Endpoints**
    - **a.** Other variables may be analyzed and presented descriptively. The methods to be used will include (but are not limited to) parametric and nonparametric analysis, means, standard deviations, frequency counts and graphs, as appropriate.
    - **b.** Video footage of patient experiences will be compiled at the end of the study. The compiled video footage will subsequently be watched and analyzed to further understand the experiences of atopic dermatitis patients, and how undergoing dupilumab treatment alters these patients' experiences and attitudes with their skin disease.

14.3 Sample Size

Up to 30 subjects will receive dupilumab for a treatment period of 52 weeks (i.e. last injection on week 50). This is based on previous similar studies investigating the impact of adalimumab and ustekinumab on QoL in psoriasis patients which included 33 and 36 patients, respectively.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic (eCRF) or paper Case Report Form when the information corresponding to that visit is available. Patient recorded videos will be downloaded to a secure storage site. Subjects will not be identified by name in the study database or on any study documents, but will be identified by a site number, subject number and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. If a correction is made on a paper CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. On eCRFs, queries are entered, tracked, and resolved through the EDC system directly. On paper, query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures;

appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the PI or a sub-investigator with the PI's

approval. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the

Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

17 REFERENCES

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APPENDIX 1. EVALUATION SCHEDULE

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time of Visit	Screening	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52
Inclusion/Exclusion criteria	X	X													
Informed consent	X														
Obtain patient demographic information	X														
Review full medical and treatment history	X														
Review interim medical history		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments*	X														
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI and IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life measures**		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other patient questionnaires***		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full-body photography (excluding face)		X				X		X							X
Instruct on proper video recording		X													
Collect and download patient videos			X	X	X	X	X	X	X	X	X	X	X	X	X
Collect, review, and record home study drug admin			X	X	X	X	X	X	X	X	X	X	X	X	X
On-site study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study meds + dosing diaries for home use		X	X	X	X	X	X	X	X	X	X	X	X	X	

* CBC with differential, CMP

** WPAI, PGWB, DLQI

*** Itch Numerical Rating Scale, Pain Numerical Rating Scale, PSQI