PROTOCOL

Study Title:	Apremilast 30 mg BID combined with Dupilumab for the Treatment of Recalcitrant Moderate-to-Severe Atopic Dermatitis
Study Drug:	Oral Apremilast 30 mg BID
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I. **Aim and Hypotheses:** The purpose of this study is to determine if apremilast as a combined treatment for atopic dermatitis will provide increased efficacy outcomes in subjects who are currently using the FDA approved therapy of dupilumab but have responded only partially or inadequately to this therapy. Our hypothesis is that adding apremilast will allow patients to go from an inadequate response to dupilumab to an adequate response defined as an Investigator Global Assessment (IGA) of 0 (clear) or 1 (almost clear).

II. **Background and rationale**:

Background and Rationale:

Dupilumab is FDA approved for atopic dermatitis and has activity against the shared alpha-chain subunit of the IL-4 and IL-13 receptor system. While type 2 inflammation is the predominant problem in atopic dermatitis, Th1 and TH17 inflammation is also part of the pathogenesis. Apremilast alone is unable to sufficiently block the dominant type 2 immune pathway in atopic dermatitis; however, apremilast can decrease multiple cytokine pathways through PDE4 inhibition. Apremilast blocks inflammatory mediators such as TNF-α, IL-12, IL-2 production in AD patients and may improve pruritus by this mechanism.[1–3] We believe adding apremilast to patients already treated with dupilumab will lead to further improvement in atopic dermatitis and select out the patient population that will most benefit from apremilast. One study using apremilast 30 mg BID versus apremilast 20 mg BID as monotherapy for atopic dermatitis saw a clinical effect after 3 months in the 30 mg BID group only.[4] We will be using apremilast in combination with dupilumab, and think the results may be synergistic.

Our hypothesis is that the addition of apremilast to dupilumab will allow patients with an inadequate response to dupilumab monotherapy to potentially achieve an Investigators' Global Assessment (IGA) score of 0 (clear) or 1 (almost clear).

2.2) Apremilast (CC-10004):
CC-10004, N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-1,3-dioxoisoindolin- 4-yl}acetamide (S-enantiomer), is a phosphodiesterase type 4 (PDE4) inhibitor. Phosphodiesterase 4 (PDE4) is a protein involved in the breakdown of cyclic adenosine 3',5-monophosphate (cAMP). [Schafer 2012 and 2014] By preventing the breakdown of cAMP, apremilast is able to enhance cAMP's ability to reduce both the T-helper 1 (Th1) and (Th2) responses that are unregulated in plaque psoriasis, resulting in improved psoriasis skin clearance.[3]

2.2.1) Pertinent human studies:

ESTEEM-1 and ESTEEM-2: The efficacy and safety of apremilast in the treatment of moderate-to-severe plaque psoriasis were evaluated in two multi-center randomized, double blind, placebo-controlled phase 3 trials of comparable design. ESTEEM-1 (n=844) and ESTEEM-2 (n=413) patients were randomized 2:1 to receive apremilast 30 mg twice daily or placebo for 16 weeks, and from Weeks 16-32, all patients received apremilast 30 mg BID (maintenance phase). The approval of apremilast was based on the data at 16 weeks from these trials. In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved an sPGA score of clear (0) or almost clear (1) at Week 16. At week 16, the proportion of patients achieving a PASI 75 response (a 75% improvement from baseline in Psoriasis Area Severity Index) was 33% of patients taking apremilast versus only 5% of placebo patients in ESTEEM-1, and 29% of patients taking apremilast versus only 6% of placebo patients in ESTEEM-2 (p

< 0.0001). Significant results were also noted in favor of apremilast for the percent change from baseline in affected Body Surface Area and PASI score, as well as the percentage of patients achieving a PASI 50. Overall, in both studies apremilast was found to be effective and associated with a favorable safety profile. The most frequently reported adverse events were diarrhea, upper respiratory tract infection, nausea, nasopharyngitis, and headache. Adverse events were mild to moderate in severity, with generally mild gastrointestinal complaints occurring early in the course of treatment and resolving with time, and there was no need for laboratory monitoring.[5,6]

PALACE 1, PALACE 2, and PALACE 3: The efficacy and safety of apremilast for the treatment of psoriatic arthritis was evaluated in 3 multi-center, randomized, double blind, placebo controlled studies of similar design. A total of 1493 adult patients with active psoriatic arthritis (PsA) (≥ 3 swollen joints and ≥ 3 tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized to placebo (n=496), apremilast 20 mg (n=500), or apremilast 30 mg (n-497) given orally twice daily. Patients were allowed to receive concurrent DMARD therapy. The primary endpoint, the percentage of patients achieving American College of Rheumatology (ACR) 20 response at week 16, was achieved by 38%, 32% and 41% of patients taking apremilast 30 mg twice daily +/- DMARDs in PsA-1, PsA-2, and PsA-3, respectively, with only 18-19% of patients on placebo +/- DMARDs achieving this response. Overall, Apremilast +/- DMARDs compared with placebo +/- DMARDs resulted in greater improvement in psoriatic arthritis symptoms and was associated with a favorable safety profile. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%).[7]

A Pilot Study of an Oral Phosphodiesterase Inhibitor (Apremilast) for Atopic Dermatitis in Adults): this open-label study tested the effects of apremilast 20 mg BID (APR20) and apremilast 30 mg BID (APR 30) in sixteen adults with atopic dermatitis. After three months, the group receiving APR20 had significant reductions in pruritus and the Dermatology Life Quality Index (DLQI), but not in the Eczema Area and Severity Index (EASI). The APR30 group had significant reductions in the EASI and DLQI.[4]

A. **Objectives:**

Efficacy Endpoints:

a. Primary Endpoint Measures:
   i. Proportion of patients who achieve an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at Week 16. Clinical improvement in a patient's eczematous lesions corresponds with a decrease in IGA, and a score of 0 (clear) or 1 (almost clear) is considered a significant clinical response.

b. Secondary Outcome Measures
   i. Proportion/percentage of subjects achieving BSA < 3%
   ii. Mean and percentage change from baseline in percent of BSA involvement
   iii. Mean and percent change of the Dermatology Life Quality Index (DLQI) from baseline
   iv. Mean and percentage change from baseline in itch on Numerical Rating Scale (NRS) pruritus scale
   v. Mean and percentage change from baseline in Eczema Area and Severity Index (EASI) score at week 16

Safety Endpoints:

Safety and tolerability will be evaluated according to the frequency and severity of adverse events and changes in physical examinations or vital signs.

II. Research Plan

A. **Overall Study Design**:
Open label phase 2 investigational study of efficacy and safety of apremilast 30 mg BID in chronic atopic dermatitis when added to the FDA approved treatment dupilumab for atopic dermatitis that is not providing adequate clinical responses. The study will have 1 phase:

- Open label treatment period apremilast 30 mg BID

Following informed consent, subjects will be screened on the basis of atopic dermatitis severity and inadequate treatment response to current therapies. IGA, BSA, pruritus NRS, EASI, complete physical examination, medical history, and concomitant medications will be reviewed. Eligible subjects will be administered treatment with apremilast 30 mg BID while continuing their prior inadequate atopic dermatitis treatment regimen. During the treatment phase, study drug will be provided in an oral form and will be titrated over 5 days and then taken twice daily thereafter. Subjects return to clinic for re-evaluation. Efficacy endpoints will be assessed at weeks 2, 4, 8, 16, and 24. Week 16 is the last week of study drug dispensation. Efficacy and safety indices will be assessed as per the Schedule of Assessments.

Treatment Assignment and Randomization
No randomization will be used, as this is an open label study. There will be no blinding and investigators will have knowledge of the treatment each subject is administered.

All patients seen in the Tufts Dermatology Clinic during the enrollment period who are not currently responding to existing FDA approved atopic dermatitis therapy and thus have not achieved a IGA of 0 or 1 at screening, and meet all other inclusion/exclusion criteria, will be offered participation in the study.

B. **Statistical methods:**

Sample size: We will screen up to 20 patients to ensure that 16 patients complete the study.

General statistical Methods: A clinical response to apremilast for the purposes of this study will be defined as an Investigator Global Assessment score of 0 (clear) or 1 (almost clear). The end points of the study will be assessed at Week 16. A period of 16 weeks was chosen, as this was the time frame utilized for primary endpoint reporting in the ESTEEM clinical program.[6,8] An additional 8 weeks of study drug will be provided to assess enhanced clinical benefit with continued use at 24 weeks. A rate of incompletion and/or drop out of subjects has been factored in to assure great than 16 patients will complete the study.

The analysis will be primarily descriptive. Mean, standard deviation, median, minimum, maximum, and 95% confidence interval for mean will be provided for continuous variables. Changes and percent changes from pre-treatment to on-treatment time points will be calculated for continuous efficacy points. Graphical displays of changes over time may be presented for key outcomes. Counts, percentages, and 95% confidence intervals will be provided for categorical variables. Subgroup analyses, such as gender stratification and stratification based on baseline treatment regimens, will be performed to identify a patient population that achieves the most benefit.

Efficacy analyses will only use data from participants who complete at least 16 weeks of study treatment in order to evaluate the primary endpoint.

Efficacy:

Primary Endpoint

Patients' Investigator's Global Assessment (IGA)[9] will be assessed at weeks 2, 4, 8, 16, and 24, with the primary endpoint being the proportion of patients with an IGA of 0 (clear) or 1 (almost clear) at Week 16.

Secondary Endpoints

Secondary endpoints will be assessed according to the scale of the outcome variable of interest. BSA and Eczema Area and Severity Index[10] will be assessed along with IGA at all study visits. For quality of life outcomes, the Dermatology Life Quality Index (DLQI)[11] will be used to assess changes from baseline in overall score will be provided. Assessment of outcomes of each protocol-scheduled time point (Weeks 2, 4, 8, 16, and 24) will be performed for each endpoint. Various schemes will be assessed for missing data imputation if needed. The change in the patient's Numerical Rating Scale for Pruritus (NRS) will be assessed.[12]

Background and demographic characteristics:

Subjects' age, weight, height and other continuous demographic and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, minimum and maximum), while gender, race and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations. Individual subject listings will be provided. A table of baseline demographic information of subjects who received study medication and controls will be provided for comparison between the two groups.

Safety:

Safety Primary Endpoints

The safety analysis will be descriptive in nature. All subjects who take at least 1 dose of the study medication will be included in the safety analyses. Safety and tolerability will be evaluated by tabulations of adverse events, which will be recorded from the time the subject signs informed consent. Adverse events will be classified on the basis of Common Terminology Criteria for Adverse Events (CTACAE) coding and summarized for each treatment. Adverse events will be summarized by system organ class, preferred term, relationship to study drug, and severity. Serious AEs and AEs leading to death or resulting in premature discontinuation will be tabulated and listed separately. Study medication-related AEs will be listed separately. Drop-out rate and reasons for early termination will be reviewed and tabulated.

Prior and concomitant medications will be reviewed and tabulated by treatment. Physical examination changes and vital signs including weight will be assessed for potential clinical significance; changes from pre-treatment to on-treatment time points will be tabulated for continuous parameters; as warranted.

Assessment of flare of atopic dermatitis will be summarized descriptively.

C. Subject Characteristics

__Inclusion criteria__:

1. Signed and dated informed consent indicating the subject has been informed of all aspects of the study
    D. Non-English speakers may be enrolled in the study in accordance with the IRB's short form policy.

2. Subject is willing and able to comply with treatment plan, study drug administration, and study protocol requirements
3. Male or females of any ethnic origin or race at least 18 years of age at time of informed consent
4. Subject has a documented clinical diagnosis of chronic atopic dermatitis for at least 6 months prior to screening visit and is a candidate for systemic therapy
5. Subjects must fulfill criteria outlined in the following clinical categories:
    - Subjects must be currently using and experiencing an inadequate response to dupilumab which is FDA approved for the treatment of moderate to severe atopic dermatitis. An inadequate response is defined as an IGA of 2 or more.
    - At the time of screening, subject must have a partial or inadequate response to their current treatment regimen. A partial or inadequate response at screening is defined as having both of the following:
        - Not having achieved an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear).
    - Subjects must be on dupilumab for at least 12 weeks and willing to continue on dupilumab on a stable dose (40 mg weekly or every other week) while also receiving the study drug
6. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

    Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

    OR

    Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.
7. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on study medication and for at least 28 days after the last dose of study medication
8. If receiving concomitant medications for any reason, must be on a stable regimen and willing to stay on a stable regimen. This includes emollients, which should stay stable throughout the study.

Exclusion criteria:

1. Prior hypersensitivity reaction or exposure to apremilast
2. Untreated or unstable depression or suicidality, including prior history of suicide attempt at any time in the subject's lifetime prior to Baseline Visit or major psychiatric illness requiring hospitalization within 3 years prior to Baseline Visit. Depression and suicidality will be assessed through standard-of-care questioning.
3. Other than atopic dermatitis, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
4. Any condition, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study

5. Subjects with a known history of CrCl<30 mL/min based on outside lab testing. No new lab testing will be performed during the study.
6. Pregnant or lactating females
7. Concomitant therapy with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin), which may cause loss of efficacy of apremilast
8. Prolonged sun exposure or use of tanning booths, which may confound the ability to interpret data from the study.
9. Active substance abuse or a history of substance abuse within 6 months prior to Screening. Subjects will be asked about any history of substance use using standard of care questioning. This will be recorded on the subject's inclusion/exclusion worksheet, which will contain the subject's study number without any other personal identifying information. Only the PI will have access to the link between the subject's ID number and identifying information. A record of the reasons for a screen-fail or other exclusion is necessary for reporting purposes to Amgen and for explanation in research publication.
10. Malignancy or history of malignancy, except for:
    - treated [i.e., cured] basal cell or squamous cell in situ skin carcinomas;
    - treated [i.e., cured] cervical intraepithelial neoplasia (CIN) or carcinoma in situ of cervix with no evidence of recurrence within the previous 5 years.
11. Use of dupilimab in combination with any other systemic immunosuppressant medication within 4 weeks prior to randomization or 5 pharmacokinetic/pharmacodynamic half lives, whichever is longer.
12. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever is longer)

Prior/Concomitant Medications

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study. As the purpose of this study is to evaluate the efficacy of apremilast 30 mg BID when combined with dupilumab, subjects must continue on a stable dose of dupilumab while also receiving the study drug.

All medications (prescription and non-prescription), treatments and therapies taken from screening through the last dose of study medication, including those initiated prior to the start of the study, must be recorded on the appropriate page of the subject documents. Record the dose, route of administration, indication, and the start and end date (when the medication was taken).

Permitted Concomitant Therapy:

The subject is required to continue on a concomitant stable dose of dupilumab treatment regimen throughout the study, given that they have been using the treatment for the minimum amount of time deemed necessary by the investigator to have experienced an inadequate clinical response. Once informed consent has been signed, subjects may not have additional atopic dermatitis medications prescribed outside of their existing atopic dermatitis treatment regimen listed at screening.

The following commonly used products are acceptable for use throughout the study: acetaminophen, loratadine, pseudoephedrine, guaifenesin, and calcium. Subjects must check with study personnel before initiating use of prescribed or over-the-counter medications during the study.

A nonmedicated emollient, i.e., Eucerin® cream (supplied by the study doctor), will also be allowed during the study; use must be stable throughout the study

Any patient found to have cellulitis on physical exam during the study will be treated with appropriate antibiotics. It is at the investigator's discretion whether the study drug will be continued or held.

Prohibited Concomitant Therapy:

- Use of any investigational medication
- Concomitant therapy with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin), which may cause loss of efficacy of apremilast
- All atopic dermatitis therapies outside of the subject's existing treatment regimen at screening are prohibited

Treatment Compliance:
Study personnel will review the instructions printed on the package insert with subjects prior to dispensing the study medication. New study medication will be dispensed according to the Schedule of Assessments. The subject will be instructed to return the study medication packaging, including any unused medication, to the study site at each visit for assessment of compliance. Subjects will be asked whether they have taken their medication as instructed at each study visit. Any problems with compliance will be reviewed with the subject.

Compliance will be assessed in two ways. Subjects will be responsible for returning unused study drug to the site. Pills will be counted to determine compliance. Subjects will also be responsible for recording the date and time they take the study drug in a medication diary. Compliance is defined as taking between 75%-125% of dispensed study medication.

Dupilumab injections will also be recorded in the medication diary.

Withdrawal/Termination criteria:
The following are considered sufficient reasons for discontinuing a subject from study drug:

- Adverse events that the investigator believes may cause severe or permanent harm or which rule out continuation of study drug
- Lack of therapeutic effect:
    - Subjects who experience a significant flare of atopic dermatitis, as defined by a sudden intensification of eczema, or as a diagnosis of erythrodermic atopic dermatitis may be discontinued from treatment and enter the observational follow- up phase of the study.
    - In addition, if the subject, in his or her opinion, feels that their disease is worsening or not responding to treatment, they may withdraw consent to participate.
- Subject withdraws consent
- Subject lost to follow-up
- Death
- Protocol violation

The reason for discontinuation will be recorded in the subject's medical records.

D. **Risk/benefit assessment**:

1. **Physical risk**: Physical risk includes potential side effects or unknown adverse events related to study medication. It is unknown how the combination of apremilast with dupilumab will affect subjects. Side effects may be worse or intensified on this combination. Subjects may be at a slightly higher risk of infection than those taking the drugs individually, but this is unknown. It is unknown if this combination will improve atopic dermatitis. AD could stay the same or get worse.
    i. The most common risks of apremilast include diarrhea, nausea, indigestion, and upper respiratory infection. Weight loss and depression have also been shown to occur.

2. **Psychological risk**: Psychological risk includes potential emotional stress related to oral administration of study medication or potential lack of improvement of atopic dermatitis

lesions.

3. **Social risk**: There are no anticipated social risks.

4. **Economic risk**: Economic risks include costs related to travel to and from study site, as well the potential costs related to obtaining the study medication such as travel to a pharmacy and insurance payments.

5. **Benefit of participating in the study**: It is unknown if the addition of apremilast to a subject's existing treatment regimen will improve the patient's atopic dermatitis. There is a potential for improvement given apremilast's efficacy in prior clinical trials for atopic dermatitis, but there is a potential the patient's condition could stay the same or worsen. Information may be obtained through this study to enable physicians to more appropriately prescribe apremilast to maximize its benefits for patients. The patient may also benefit from checking vital signs at screening and follow up visits.

<u>**Study Drug Materials and Management**</u>

Supplier: Amgen will supply all study medication to the principal investigator.

Dosage Regimen: Apremilast will be administered to patients as 30 mg oral tablets taken twice daily for 24 weeks. An initial 5-day titration will be implemented to improve tolerability. The study drug will be started the morning of Day 1 at 10 mg. On Day 2, the study drug will be taken at 10 mg in both the morning and evening. On Day 3, the study drug, will be taken at 10 mg in the morning and 20 mg in the evening. On Day 4, the study drug will be taken at 20 mg in both the morning in evening. On Day 5, the study drug will be taken at 20 mg in the morning and 30 mg in the evening. On Day 6 and thereafter, the study drug will be taken at 30 mg in morning and evening. Doses should be 12 hours apart. Subjects will be instructed that apremilast can be taken with or without food and that the tablets should not be crushed, split, or chewed. Subjects will also be instructed to store tablets below 30°C (86°F). Subjects will simultaneously continue on their prior atopic dermatitis treatment regimens in addition to taking apremilast. If a subject misses a dose of the study drug, they may take it as soon as they remember, as long as it is more than 6 hours before the next scheduled dose. In this case, the subject will take the missed pill, and then take their next pill at their usual dosing time and resume their normal dosing schedule. If the subject forgets to take a dose and it is <6 hours before their next scheduled dose, they should not take the forgotten pill and should not double-dose. Subjects should take their next scheduled dose at their usual time and resume their normal dosing schedule. Subjects will be responsible for recording the dates and times that they dose, and mark any missed dose as "missed" in their dosing diary. Treatment compliance will be assessed as described on page 8 of the protocol.

Record of administration: Accurate recording of all study drug administration (including dispensing and dosing) will be made in the appropriate section of the subject's source documents.

Study Medication Accountability: The investigator or designee(s) is responsible for accounting for all study medication that is issued to and returned by the subject during the course of the study. If any study drug is lost or damaged, its disposition should be documented in the subject's source documents.

E. **Specific methods and techniques used throughout the study**:

1. **Study Procedures**: At the initial visit, a Investigator's Global Assessment (IGA) of disease will be performed to determine if the patient meets the inclusion criteria. A score on the NRS Pruritus

scale will be determined. A thorough medical history and a review of prior/concomitant medications will be taken at the screening visit. A complete physical examination including weight and vital signs (temperature, blood pressure) will also be performed. At the following visits according to the Schedule of Assessments, a IGA, BSA, DLQI survey, vital signs, NRS pruritus scale, EASI, a complete or targeted physical exam and review of concomitant medications and adverse events will be performed. Additionally, drug dispensing and accountability will also occur at all visits after the screening visit according to the Schedule of Assessments.

- Lab monitoring is not standard of care for patients using apremilast in clinic settings for the treatment of psoriatic disorders. Patients with psoriasis are frequently prescribed apremilast in addition to psoriasis biologic injectables, and it is not standard of care to perform lab tests for these patients that is outside of what is recommended for monitoring the safety of their injectable biologic alone. Atopic dermatitis patients taking apremilast are not at any increased risk compared to psoriasis patients taking apremilast. Dupilumab is a biologic, but this specific biologic does not require lab monitoring. For these reasons, lab monitoring will not be performed during this study as it would cause research subjects to undergo unnecessary testing.However, for all patients taking apremilast, it is standard of care to monitor weight at treatment visits and to ask patients about adverse symptoms. Both of these will be performed during the study based on the schedule of assessments.

2. **Subject Timeline**: 24 week duration of study treatment.

F. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

- AE data will be collected at each study visit by asking the subject about their symptoms. The PI will review all AE data as they are collected, and the PI will sign off on AEs during the study visit. The AEs for the subjects will be stored in the subject's study documents and updated at each study visit. AEs will be collected from the time of ICF signature through the end of the study at all study visits.
- AEs of Special Interest such as infections and malignancies will be reviewed ongoing throughout the study as they are reported. In the instance that there are 3 serious related infections or 2 new malignancies (excluding non-melanoma skin cancers) the PI will place a pause on enrollment until further evaluation is conducted.
- At the end of the study, all AE data collected in the subjects' study documents will be compiled into an excel spreadsheet where the data will be analyzed by the PI. There will be no interim review of these data (with the exception of AEoSI).
- The PI may terminate individual subjects from the trial if he determines that the subject's safety is at risk due to their AE.
- <u>Definition of Serious Adverse Event (SAE) and Adverse Event (AE) for this study</u>: All observed or volunteered adverse events regardless of suspected causal relationship to the investigational product would be recorded. An adverse event is any untoward medical occurrence in a subject administered a clinical investigation medication. Examples include progression/worsening of underlying disease, abnormal test findings, changes in vital signs or physical examination findings, and clinically significant symptoms and signs. The investigator and/or site staff will determine if the adverse event meets criteria for a significant adverse event.

A significant adverse event is any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization, results in significant disability, or results in congenital anomaly or birth defect.

- It is at the discretion of the PI and sponsor whether an SAE requires the termination of the research.

- Reporting timeframe for SAEs and AEs: AE's will be recorded in the subject's patient chart as they occur. The subject will detail all information pertaining to adverse events noted during the study, including date of onset, date of resolution, severity, and relationship to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Amgen Global Safety by facsimile. A written report (prepared by the Investigator(s) using an SAE Report Form or a 3500A MedWatch form is to be faxed to Safety (see below for contact information).

Amgen Safety Contact Information:
Amgen Global Drug Safety
Fax: 1-888-814-8653
E-mail: svc-ags-in-us@amgen.com

Reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's Reportable New Information policy.

- Accountability procedures as they relate to drugs, devices, and data: The investigator or designee(s) is responsible for accounting for all study medication that is issued to and returned by the subject during the course of the study. If any study drug is lost or damaged, its disposition should be documented in the subject's source documents.
- The study drug will be stored in the investigational pharmacy. IDS will be responsible for dispensing medication. All unused drug will be returned to IDS at the end of the study. The research coordinator is responsible for communicating with IDS. The PI is responsible for signing all drug order forms.

Contraception Education

The risks to a fetus or to a nursing child from apremilast are not known at this time. Results of the animal and in vitro studies can be found in the IB.

All females of childbearing potential (FCBP) must use one of the approved contraceptive options as described in section II:C:6 while on investigational product and for at least 28 days after administration of the last dose of the investigational product.

When a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes at the time of study entry or at any time during the study, the Investigator will educate the subject regarding options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Safety immediately facsimile using the Pregnancy Report form provided by Amgen. An authorization form to request the collection of this information from the pregnant partner of a male subject will be submitted to the IRB for review and approval prior to the collection of this information. The study team will request that subject approach their pregnant partner to obtain authorization, and the pregnant partner may contact the study team for more information.

G. Subject Participation

1. **Recruitment**: Recruitment will occur through the outpatient dermatology clinic at Tufts Medical Center once IRB approval is obtained. Goals for recruitment in terms of screening treatment regimens include: 16 subjects completing the study. Up to 20 may be screened to allow for screen fails.
    - Dermatologists in the TMC department of dermatology will be informed about the ongoing trial and its key inclusion/exclusion criteria. Dermatologists can inform their patients about the study during the patient's regular scheduled clinic visit. If a patient is interested, research staff will come down to the dermatology clinic to inform the patient further. If the subject chooses to proceed with a screening visit, this will be conducted in a private research room where informed consent will be obtained. Alternatively, the screening visit can be scheduled for a future date. Dermatologists may also tell their patients about this study and provide research staff contact information to the patient
    - The clinical recruitment website will provide online information about the study. Additionally, this trial will be listed on clinicaltrials.gov. Study team contact information will be provided in both of these websites, and interested subjects may call the department for more information. There are no other recruitment materials.
    - These two methods have been effective in the past for our recruitment of other investigator-initiated trials of similar sample sizes.

2. **Registration**: Not applicable.

3. **Screening Interview/questionnaire**: Screening will occur once subject has had ample time to review and sign the informed consent form. The screening visit will be performed by Dr. David Rosmarin and other qualified research staff members at the Tufts Medical Center Dermatology Research Department.

4. **Transportation**: Subjects will arrange for their own transportation to and from the Tufts Medical Center.

5. **Informed consent process and timing of obtaining of consent**: Providing detailed and comprehensive information about the study and obtaining written informed consent will be done by Principal Investigator or other qualified research staff members prior to any study-related procedures. Subjects will have adequate time to review informed consent, ask site staff questions, discuss study participation with their family or friends, and then sign informed consent if they choose to participate in the study. Explaining the study, answering of questions, and obtaining written consent will be carried out in a private patient room to ensure patient

confidentiality. The original consent form signed and dated by the subject must be maintained in the investigator’s study files and a copy given to the subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent. The revised consent form signed and dated by the subject and by the person consenting the subject must be maintained in the investigator’s study files and a copy given to the subject.

6. .**Location where study will be performed**: The study will take place at the Dermatology Clinic at Tufts Medical Center.

7. **Personnel who will conduct the study, including**: All personnel with delegated responsibilities will have completed appropriate GCP and CITI training for biomedical research.

    - The PI is a board-certified dermatologist with over a decade of clinical and research experience. He currently serves as the PI for all our active research studies, as well as past research studies that are currently closed.
    - Nicole Dumont is a skilled research-coordinator with almost two decades of experience in our department as the coordinator. She served as the coordinator for all of our active and past studies.
    - Courtney Kachuk is a registered nurse with a decade of experience in our department as the study nurse. She has delegated responsibility as the study nurse in all our active trials and past trials.
    - There will be no sub-PI for the study; all visits will be scheduled on a day when the PI is present at the study site.
    - Research fellows listed on the IRB Form 1 as involved with this study include current TUSM students and international MD holders. All research fellows have clinical experience. Fellows will not be added to the research team or the delegation log of this study until they have been adequately trained. Training will be provided by the research coordinator and study nurse, who will delegate responsibilities at their discretion. The IRB will be informed of any additions to the research team.
    - The entire research team will be trained in the protocol, their roles and responsibilities, before initiation of the trial. If new members are to be added to the research team, it is the responsibility of the research coordinator to provide ongoing training.

    a. **Present during study procedure(s) and their proximity during the study**: David Rosmarin MD, Nicole Dumont, Courtney Kachuk, RN, Research fellows listed as members of the research team on the IRB Form 1.

    b. **Primary responsibility for the following activities**:

    i. **Obtaining informed consent**: David Rosmarin, MD
    ii. **Providing on-going information to the IRB**: David Rosmarin, MD, Nicole Dumont,

    iii. **Maintaining participant's research records**: David Rosmarin, MD, Nicole Dumont, Courtney Kachuk, RN

8. **Subject fees**: There will be no direct subject fees and no reimbursement fees.

9. **Study results**: The only results that will be given to the patient are abnormal vital signs, in which case the site staff will discuss the abnormal results and schedule appropriate follow up.

10. **Procedures to protect subject confidentiality**: Subject information will be documented and safely protected in Tufts Dermatology medical center in locked cabinets which only the investigator and permitted research staff will have access to. All data collected at study visits will be stored on password-protected computers in locked rooms.

    - All visits will take place in a private research room in the department of dermatology. Study procedures will be explained to subjects in language that is appropriate for their educational level and medical understanding. Subjects will interact with a small group of research staff for their entire participation in the study, who will introduce themselves to the subjects at the beginning of the study and as procedures need to be performed.

11. **Confidentiality**:

    a. **Certificate of Confidentiality**: This will be obtained if necessary and as per Tufts Medical Center IRB regulations.

    b. **How data will be coded, recorded, and stored to protect confidentiality**: The Principal Investigator will code all subject samples with a unique code number. Only Principal Investigator and site staff will be able to link code number to subject name. Data will be recorded through code number and stored in a locked cabinet in locked office in research department office. The investigator must ensure that the records and documents pertaining to the conduct of the study and distribution of the study drug are complete, accurate, and filed and retained. The "Confidentiality and Data Security Guidelines for Electronic Research Data" for electronic data will be followed. Data will be stored and maintain for 7 years after study closure with the IRB and as described in the record retention policy of the "SOP – Records Retention Timeframe – Investigators".

    c. **Parties who will have access to the data, including the key to the identity code**: Principal Investigator and research staff.

    d. **Parties who will have access to research records:** The subject's right to protection against invasion of privacy will be upheld throughout the study. In compliance with United States federal regulation, only permitted research staff will have access to subject's medical records, and when necessary, representatives of the FDA or other regulatory authorities to review and/or copy and medical records relevant to the study in accordance with local laws.

12. Collaboration: Data will be available to principal investigator, site staff, Amgen, Institutional Review Board of Tufts Medical Center, and potentially certain government agencies such as the U.S. Food and Drug Administration. Otherwise, there is no collaboration with another institution.

13. **Alternatives**: An alternative is not to participate in the study. In the event the subject decides not to participate, the principal investigator and/or site staff can discuss other treatment options for plaque atopic dermatitis with the patient including the following:
    a. Continuation of existing regimen without participation in this study

b. Topical medications such as corticosteroids (triamcinolone, clobetasol, etc.), topical calcineurin inhibitors (tacrolimus, Protopic, etc), and Eucrisa (crisaborole)
c. Oral medications for eczema include steroids (Prednisone, etc.), or immunosuppressants (CellCept, cyclosporine, etc.).
d. Participation in a different clinical trial for another investigational product
e. The study drug, apremilast, is not available at this time for atopic dermatitis. It is currently approved for the treatment of psoriasis and psoriatic arthritis. Dermatologists may attempt to gain insurance coverage for off-label prescribing of this medication for AD at the end of the study. Dupilumab is currently standard of care for AD, and can be prescribed at the end of the study by the subject's regular dermatologist

14. **How new information will be conveyed to the study subject and how it will be documented**: New information will be conveyed through IRB approved amendment to the Informed Consent form.

15. **Payment, including a prorated plan for payment**: Subjects will be paid $50.00 per visit for this study. Subjects will be paid via clincard. Subjects will be paid after each visit attended. Subjects will not be paid for any missed visits. Subjects can make up to $300.00 for completion of the entire study.

16. **Payment for a research-related injury**: Research related injuries at not anticipated in this study and if an injury does occur, an appropriate plan of action will be determined by principal investigator at that time.

I. **Outcome**: Study results and outcomes will be prepared in a manuscript for peer-reviewed journal publication. Success will be determined as described above in the "objectives" section.

J. **Tissue banking considerations**: Not applicable.

Schedule of Assessments

Protocol Activity	Visit 1: Screening/ Baseline[1]	Visit 2 Week 2 ± 3 days	Visit 3 Week 4 ± 3 days	Visit 4 Week 8 ± 3 days	Visit 5 Week 16 ± 3 days	Visit 6 Week 24 ± 3 days	Early Termi-nation
Informed Consent	X						
Atopic Dermatitis diagnosis, medical history	X						
Concomitant/prior Medications	X	X	X	X	X	X	X
Complete physical examination[2]	X						X
Targeted physical examination[3]		X	X	X	X	X	
Vital signs (Temperature, resting pulse, seated blood pressure)	X	X	X	X	X	X	X
Demographic information[4]	X						
CLINICAL EVALUATION							
Assessment of atopic dermatitis[5]	X						
Investigator's Global Assessment of disease (IGA)	X	X	X	X	X	X	X
Body Surface Areas (BSA)	X	X	X	X	X	X	X
NRS Pruritus scale	X	X	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X	X	X	X	X	X
Photography	X	X	X	X	X	X	X
PATIENT REPORTED OUTCOMES							
Dermatology Life Quality Index (DLQI)	X	X	X	X	X	X	X
OTHER ACTIVITIES							
Study Drug Dispensing	X		X	X	X		
Drug Accountability		X	X	X	X	X	X
Adverse Event Reporting		X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X
Urine pregnancy test[6]	X	X	X	X	X		

[1] Baseline visits may occur at the same time as the screening visit, or within 4 weeks of the screening visit.

[2]Complete physical examination includes weight, general appearance, skin, HEENT (head, eyes, ears, nose, throat), heart, lungs, abdomen, lower extremities, neurologic and lymph nodes. Height will be recorded at screening only.
[3] Targeted physical examination consists of weight, examination of heart, lungs, abdomen, lymph nodes, and lower extremities, as well as any area of patient-reported AEs.
[4] Demographic information including but not limited to age, race, gender, ethnicity
[5] For study eligibility, subjects must have active atopic dermatitis at Screening, which has been diagnosed or confirmed by a dermatologist.
[6] Urine pregnancy test (human chorionic gonadotropin; HCG) is required only for women of child-bearing potential

Assessments of Efficacy:

- **Investigators Global Assessment (IGA)**
- **Body surface area** (BSA) of involved skin will be measured at Screening, Baseline, and at following visits according to the Schedule of Assessments until study completion.
- **Numerical Rating Scale (NRS) Pruritus Scale**
- **EASI**
- **DLQI**

Assessments of Health-Related Quality of Life:

- **Dermatology Life Quality Index** will be assessed by the subject at Day 1, and Weeks 2, 4 8,
- 16, and 24 upon arrival at the site before any other procedures or assessments are performed.
  The DLQI is a self-administered, 10-item questionnaire measuring the impact of skin disease on subjects' quality of life based on recall over the past week. Domains include symptoms, feelings, daily activities, leisure, work, personal relationships, and treatment. Possible responses for each of the 10 items include: not at all, a little, a lot, and very much. Each question is scored on a scale of 0 to 3 with a total range of 0 to 30.[11]

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes	❒	
		No	❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	❒	
		A little	❒	
		Not at all	❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒

10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much	❒	
		A lot	❒	
		A little	❒	
		Not at all	❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

IGA

7.6.2. 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 3. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 3. 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.

EASI

Score		Description*
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

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

Percent BSA with Atopic Dermatitis in a Body Region	Area Score
0%	0
>0 - <10%	1
10 - <30%	2
30 - <50%	3
50 - <70%	4
70 - <90%	5
90 - 100%	6

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin/genitals)	0.3
Lower Limbs (including buttocks)	0.4

* No adjustment for body regions excluded for assessment

NRS-Pruritis

Severity of Pruritus

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

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No itch										Worst itch imaginable

Frequency of Pruritus

Select the number that best describes frequency of itching due to Atopic Dermatitis over the past 24 hours (check one number only).

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Never /No itching										Always/constant itching

References

1. Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, Gold LS. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8(8):853-866. doi:10.2217/imt-2016-0023
2. Dong C, Virtucio C, Zemska O, et al. Treatment of Skin Inflammation with Benzoxaborole Phosphodiesterase Inhibitors: Selectivity, Cellular Activity, and Effect on Cytokines Associated with Skin Inflammation and Skin Architecture Changes. *J Pharmacol Exp Ther*. 2016;358(3):413-422. doi:10.1124/jpet.116.232819
3. Bäumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets*. 2007;6(1):17-26. http://www.ncbi.nlm.nih.gov/pubmed/17352685. Accessed January 16, 2019.
4. Samrao A, Berry TM, Goreshi R, Simpson EL. A Pilot Study of an Oral Phosphodiesterase Inhibitor (Apremilast) for Atopic Dermatitis in Adults. *Arch Dermatol*. 2012;148(8):890-897. doi:10.1001/archdermatol.2012.812
5. Papp KA, Bissonnette R, Gooderham M, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a Phase 2b randomized clinical trial. *BMC Dermatol*. 2016;16(1):15. doi:10.1186/s12895-016-0051-4
6. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173(6):1387-1399. doi:10.1111/bjd.14164
7. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. 2014;73(6):1020-1026. doi:10.1136/annrheumdis-2013-205056
8. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73(1):37-49. doi:10.1016/j.jaad.2015.03.049
9. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. *J Am Acad Dermatol*. 2016;74(2):288-294. doi:10.1016/j.jaad.2015.09.062
10. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-18. http://www.ncbi.nlm.nih.gov/pubmed/11168575. Accessed January 16, 2019.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. http://www.ncbi.nlm.nih.gov/pubmed/8033378. Accessed November 8, 2018.
12. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2017;76(6):AB278. doi:10.1016/j.jaad.2017.04.1082