CLINICAL STUDY PROTOCOL

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A PHASE 2, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-COHORT STUDY INVESTIGATING THE EFFECT OF EDP1815 IN PARTICIPANTS FOR THE TREATMENT OF MILD, MODERATE AND SEVERE ATOPIC DERMATITIS

PROTOCOL EDP1815-207

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LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse Event
ALT	Alanine Aminotransferase
APP	Application
AST	Aspartate Aminotransferase
BSA	Body Surface Area
CDMS	Clinical Data Management System
CI	Confidence Intervals
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DPS	Data Point Set
EC1 or EC2	Enteric Coating
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
EASI	Eczema Area and Severity Index
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
LS	Least Squares Mean Estimate
mL	Milliliter
MMRM	Mixed Model for Repeated Measures
OLE	Open Label Extension
PBMC	Peripheral Blood Mononuclear Cell
PP-NRS	Peak Pruritus Numerical Rating Scale
RNA	Ribonucleic Acid
SD-NRS	Sleep Disturbance Numerical Rating Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SF-12	12-Item Short Form Health Survey
SLS	Sodium Lauryl Sulfate
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TMF	Trial Master File
ULN	Upper Limit of Normal
vIGA or IGA	Validated Investigator Global Assessment
WGS	Whole Genome Sequencing
WOCBP	Woman of Child-Bearing Potential

PROTOCOL SUMMARY

Study Objectives: The primary objective is to show superiority of EDP1815 over placebo in the treatment of atopic dermatitis. The secondary objectives are to further evaluate the efficacy, safety and tolerability of EDP1815. Exploratory objectives aim to evaluate the best daily dose and frequency of dosing for EDP1815 in the treatment of atopic dermatitis, the time to onset of clinical response to EDP1815 and the effect of EDP1815 treatment on blood biomarkers.

Primary endpoint: The Eczema Area and Severity Index (EASI) will be utilized to measure the extent and severity of a participant's atopic dermatitis. The percentage of participants achieving EASI-50 (percentage of participants with a ≥ 50% reduction in EASI score from baseline) at Week 16 will be utilized to evaluate the efficacy of EDP1815 over placebo. Participants requiring use of topical corticosteroid rescue therapy less than 28 days before the Week 16 visit or who withdraw from the study prior to the Week 16 visit for reasons considered related to study treatment will be considered as non-responders.

Secondary endpoints: The EASI Score will also be utilized to measure other aspects of clinical benefit of EDP1815 in the treatment of atopic dermatitis. In addition to EASI, the Validated Investigator's Global Assessment (vIGA), the body surface area (BSA) of skin affected by atopic dermatitis, the SCORing Atopic Dermatitis (SCORAD), the use of Rescue Medications, the Dermatology Life Quality Index (DLQI), the Peak Pruritus Numerical Rating Scale (PP-NRS), the Sleep Disturbance Numerical Rating Scale (SD-NRS) and the Patient Oriented Eczema Measure (POEM) will be measured throughout the study.

The severity and frequency of Adverse Events will be used to evaluate the safety and tolerability of EDP1815.

Exploratory endpoints: A number of exploratory endpoints will be evaluated to determine further aspects of treatment efficacy including time to achieve clinical response and patient reported health outcomes. Changes in eosinophils, immune protein markers and immune cell RNA profile will be used to evaluate the effect of EDP1815 treatment on biomarkers in blood. A fecal sample will be used for microbiome profiling. Human Leukocyte Antigen (HLA) typing will be performed in those participants who consent to assess the correlation with clinical outcomes.

Brief Study Design: This study will evaluate EDP1815 in participants with mild, moderate, and severe atopic dermatitis, to compare efficacy, safety, and tolerability to placebo. The Investigational Medicinal Product (IMP) is EDP1815 or matching placebo. The study will be blinded to the participants, Investigator, and Sponsor.

Approximately 405 participants will be randomized to receive either EDP1815 or placebo (295 to EDP1815: 110 to placebo) and treated for 16 weeks. Following end-of-treatment assessments, participants may enter a 4-week post-treatment follow-up period or may elect to participate in an Open Label Extension (OLE) Protocol for EDP1815, if available. Cohorts 1, 2 & 3 will be run concurrently, and Cohort 4 recruitment will commence after enrollment for Cohorts 1, 2, & 3 are completed.

Participants will be dosed with EDP1815 or matching placebo administered as the following:

- **Cohort 1:** $1.6x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 2:** $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 3:** $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 1 capsule of $3.2x10^{11}$ cells twice daily.
- **Cohort 4:** $8.0x10^{10}$ total cells of EDP1815 or matching placebo administered as 1 capsule once daily.

Participants in Cohorts 1, 2, & 3 will be randomized in a 3:1 ratio (225 to EDP1815: 75 to placebo). Participants in Cohort 4 will be randomized in a 2:1 ratio (70 to EDP1815: 35 to placebo). Randomization to Cohort 4 will not start before randomization to Cohorts 1, 2 & 3 have completed.

An interim analysis may be performed just before the end of recruitment to Cohorts 1, 2 & 3 to check the assumptions used for the sample size calculation and to ensure that there is no imbalance between treatment groups caused by incomplete randomization blocks.

The data collected for Cohorts 1, 2 & 3 may also be locked and analyzed prior to the completion of Cohort 4.

Study Duration: The maximum study duration is up to 24 weeks for all participants. Following informed consent, participants will have up to a 4-week screening period, followed by a 16-week treatment period and a post treatment follow-up visit 4 weeks later. Should a participant elect to participate in the Open Label Extension (OLE protocol), their study duration during this study would be a maximum of 20 weeks.

1. INTRODUCTION

1.1. Atopic Dermatitis

Atopic dermatitis (AD), also known as (atopic) eczema, is a chronic, highly symptomatic relapsing inflammatory skin disease, affecting up to 30% of children and 10% of adults (Bieber, Atopic Dermatitis, 2010). While AD often begins in infancy or childhood, it may become chronic and persist into adulthood (Katoh, 2019). Depending on factors such as severity of skin lesions or body surface area coverage, the disease can be classified clinically as mild, moderate, or severe.

Patients with AD typically have highly symptomatic skin lesions that may present acutely with erythema, exudates, papulovesicles, scales and crusts, often symmetrically distributed on the body (Katoh, 2019). The disease typically follows a variable course with acute flares, often triggered by external factors, which cause a worsening of skin disease and symptoms. More chronic lesions are associated with thickened lichenified skin which may be accompanied by pigmentary changes and further excoriations (Bieber, Atopic Dermatitis, 2010). The primary symptom at both stages of disease is typically pruritus (itch). Such signs and symptoms are associated with a substantial patient burden that typically includes sleep disturbance, mood disturbance and mental health problems (Simpson, 2012), poor quality of life, and social functioning (Kiebert, 2002).

AD, like other atopic disease, is characterized by a T helper type 2 (Th2) cell-mediated inflammation, with up-regulation of Th2 cytokines including IL-4, IL-5, and IL-13 (Indra, 2013). In turn, this leads to increased IgE production by B-cells, which can trigger release of cytokines and chemical mediators such as histamine from mast cells and Langerhans cells. In addition, thymic stromal lymphoprotein is thought to be a critical cytokine in the triggering and maintenance of AD (Indra, 2013), and is associated with migration of Th2 cells into the skin lesion (Katoh, 2019). The resulting systemic inflammation drives the disease pathology and patient symptoms, with the resultant scratching of pruritic lesions further worsening the skin lesions and the skin barrier function, further driving the disease process. Therefore, targeting systemic inflammation improves disease signs and symptoms – for example systemic corticosteroids typically lead to rapid clinical improvements, but generally are not acceptable as a long-term treatment due to associated side-effects (Lee, 2016).

In general, treatment of AD is aimed at a combination of resolution of skin disease and improvement of symptoms such as itch (acute therapy), and also prevention of further flares (maintenance therapy). Emollients, also known as moisturizers, are the first-line and baseline therapy for all severities of disease, and act by treating the defective skin barrier and providing cutaneous hydration (Lee, 2016). There are a number of other topical treatments including topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) (Katoh, 2019). Unfortunately, there are associated problems with such treatments including adverse effects, limitations in efficacy, and low patient acceptability and tolerability, particularly when used as chronic treatment options.

In the US, there are currently no licensed oral treatments for atopic dermatitis; while in the European Union, only ciclosporin is licensed as an oral treatment. Due to its associated risks and side-effects, such as renal failure, ciclosporin is generally only recommended for short-term use (Katoh, 2019). Other anti-inflammatory treatments, such as methotrexate or azathioprine, are therefore used off license in order to reduce the Th2-driven systemic inflammation. These systemic

treatments all have associated risks and side-effects and are therefore not suitable for a large population of patients, including many of those with mild and moderate disease. Finally, for patients with moderate-to-severe disease, Dupixent (dupilumab) is now licensed as a biologic injectable treatment and is currently used to treat a small proportion of patients with such disease severity.

A 2016 patient survey (National Eczema Association, 2016) highlights and summarizes what it is like for patient living with atopic dermatitis:

- 84% are "very" or "extremely" bothered by dry skin, 83% by itch, and 63% by rash/redness
- 75% stated AD interferes with their job and house chores, 71% say it interferes with hobbies, and 65% don't feel as healthy because of AD
- Nearly half of people with moderate to severe AD report their disease "interferes with their social life, intimate relations, and relationships with their spouse and children"
- 1 in 3 takes one or more hours per day to treat their AD
- More than half are dissatisfied overall with each of the following treatments that they are using or have used: topical steroids, topical calcineurin inhibitors, phototherapy, and oral medications

The conclusion from this study was that there is a "lack of safe and effective treatments" for AD, allowing for "unchecked symptoms [which] contribute to the range of health issues". This sums up the unmet need for and importance of further oral treatments for AD.

1.2. Previous Experience with EDP1815 and Rationale for Treating Atopic Dermatitis

Evelo Biosciences, Inc. (Evelo) is developing orally administered biologic medicines based on a new understanding of how immunity and inflammation are controlled. Evelo's medicines are selected for their ability to modulate the small intestinal axis (SINTAX™). This is the network of anatomical and functional connections that has evolved to link the small intestine and the rest of the body. It links small intestinal mucosal immunology with systemic inflammation and is accessible with oral SINTAX medicines.

The inflammatory control mechanisms of SINTAX down-regulate multiple inflammatory pathways including those which have been validated with targeted antibody therapies, but without the side effects seen with antibody therapeutics or broadly acting oral kinase inhibitors. This occurs via specific interactions between the oral SINTAX therapy and small intestine enterocytes and immune cells. These interactions drive the development of an immune-regulatory subset of lymphocytes that travel from the gut to the systemic circulation, via the mesenteric lymph nodes. Here, these circulating cells mediate their effects on peripheral inflammation at the target sites (e.g., atopic dermatitis skin).

EDP1815 is a pharmaceutical preparation of a single strain of *Prevotella histicola*, originally isolated from a duodenal biopsy. The drug substance is essentially non-viable and non-replicating, with a cell viability of <0.02%. It has not been genetically modified. It does not colonize the gut nor alter the microbiome and has no detectable systemic exposure following oral dosing to date – i.e., it is gut-restricted.

Prevotella as a genus are gram-negative, obligate anaerobic bacteria that are natural human commensals found in the oral cavity and gastrointestinal (GI) tract. Strains of *Prevotella* have been found in all human populations tested to date, at abundances ranging from <1% to nearly 50% of total fecal microbial load (Vandeputte, Kathagen, & D'hoe, 2017).

In vitro studies of EDP1815 in human and mouse cellular assays and in vivo models support its use in the treatment of immunoinflammatory diseases, including atopic dermatitis. Oral administration of EDP1815 to mice led to striking therapeutic effects on delayed-type hypersensitivity (DTH), imiquimod-induced skin inflammation, fluorescein isothiocyanate (FITC) cutaneous hypersensitivity, collagen-induced arthritis (CIA) (Marietta, Murray, & Luckey, 2016) and experimental acute encephalomyelitis (EAE) (Mangalam, Shahi, & Luckey, 017) in-vivo models. EDP1815 was shown to down-regulate key Th2-related cytokines including IL-4 and IL-31. No potentially related adverse effects were seen in the animals used in these experiments with daily dosing for up to 3 weeks, or alternate day dosing for over 7 weeks. Ex vivo immunophenotyping in these models shows increased regulatory T cell numbers and regulatory dendritic cells (DCs) in spleen and mesenteric lymph nodes, as well as decreases in pro-inflammatory cytokines such as IL-23 p40, IL-17, and IL-13. EDP1815 does not suppress the expression of Type1 interferons in these ex vivo experiments, suggesting that the broad spectrum of anti-inflammatory effects is achieved without damaging mechanisms of immune surveillance critical for avoiding cancers and pathogens. Treatment also led to enhancement of gut intestinal barrier integrity, which is often disrupted in patients with inflammatory diseases. The effects on immune parameters have been observed both within and outside of the GI tract, which demonstrates that host-microbe interactions in the gut can affect the immune response in peripheral tissues.

This pre-clinical data therefore supported advancing EDP1815 into the treatment of atopic dermatitis, due to the resolution of systemic inflammation including in models of Th2-driven disease, and the reduction of Th2-dervied cytokines that are known to drive the pathophysiology of atopic dermatitis.

Clinical data is accumulating that supports both the role of the small intestinal axis in humans and that it can be harnessed by EDP1815 as a potent modulator of systemic inflammation, in Th1, Th2 and Th17 inflammation. As of September 2021, a total of 623 adult participants have been exposed to EDP1815 or placebo. A total of 458 participants received EDP1815: 54 healthy volunteers, 234 patients with mild to moderate psoriasis, 48 patients with mild to moderate AD and 122 patients with COVID-19 infection. A total of 165 subjects received placebo: 16 healthy volunteers, 117 patients with mild to moderate psoriasis, 24 patients with mild to moderate AD and 8 patients with COVID 19 infection. To date, EDP1815 is well tolerated with a safety profile comparable to placebo – there are no AEs of special interest and no related serious adverse events have been seen.

In the phase 1b study EDP1815-101, 16 participants in cohort 7 were treated with EDP1815 capsules at a dose of 8.0 x 10^{11} cells once daily for 8 weeks, with a further 8 participants given matching placebo. Clinically meaningful and significant responses were observed at the end of the treatment period, in terms of the changes in EASI, vIGA*BSA and SCORAD, as well as within the patient-reported outcomes, which also found improvements in itch and sleep scores.

The available evidence to date has found EDP1815 to be very well tolerated with evidence for proof of concept as an effective treatment for atopic dermatitis. A well tolerated oral therapy could offer significant benefit in atopic dermatitis for all severities of disease.

2. STUDY OBJECTIVE(S)

2.1. Primary Objectives

The study will compare four treatment regimens of EDP1815 with placebo in participants with atopic dermatitis who are using twice daily topical emollients.

The primary comparison of interest is the odds ratio for achievement of an EASI-50 response at Week 16. The primary trial objective is to show superiority of EDP1815 over placebo.

The primary comparison will be made using a treatment policy strategy with respect to study medication but without regard to treatment compliance or any changes in background therapy. A composite strategy will be used with respect to use of topical corticosteroid rescue therapy with any participants who use these less than 28 days prior to the Week 16 assessment being considered as non-responders. A composite strategy will also be used for participants who withdraw from the study prior to the Week 16 visit for reasons relating to study medication (e.g., related adverse event, lack of efficacy, requirement of for alternative therapy) also being considered as non-responders. A 'while on treatment' strategy will be used for participants who withdraw from the study prior to Week 16 for reasons considered unrelated to study medication, with the achievement of response at Week 16 being considered missing.

A number of supportive analyses to check the robustness of the primary estimand approach will be performed. These will consider

- Topical corticosteroid rescue therapy in the window of 2-4 weeks prior to study medication as having no effect and using the composite strategy only for use less than 14 days prior to the Week 16 visit
- Using a 'while on treatment' strategy for rescue medications with any Week 16 data collected less than 28 days after rescue medication use being considered missing.
- Using a 'while on treatment' strategy for discontinuation of the study for any reason before Week 16.
- Using a principal stratum strategy excluding participants who are non-compliant with respect to study medication or emollient use (<75% compliance), use a prohibited background therapy, take at least one dose of the incorrect study medication or who are unblinded prior to the end of the study.
- Using an alternative composite strategy for topical corticosteroid rescue therapy, with all participants who use any topical corticosteroid therapy at any time between Day 1 and Week 16 considered as non-responders at the Week 16 visit.

2.2. Secondary Objectives

The secondary objectives of this study are the following:

1. To evaluate the clinical benefit of EDP1815 in the treatment of atopic dermatitis.

2. To evaluate the safety and tolerability of EDP1815.

These objectives will be evaluated using a treatment policy approach with respect to study medication and a composite approach with respect to use of topical corticosteroid rescue therapy within 4 weeks. Full details can be found in **Section 11 Statistics**.

2.3. Exploratory Objectives

The exploratory objectives of this study are the following:

1. To evaluate the time to onset of clinical response to EDP1815.
2. To evaluate the most effective dose and dosing frequency of EDP1815 in the treatment of atopic dermatitis.
3. To evaluate the effect of EDP1815 on patient reported outcomes.
4. To evaluate the effect of early use of rescue therapy on Week 16 responder status.
5. To evaluate the relationship of EDP1815 treatment with biomarkers such as immune protein markers, eosinophils, and immune cell RNA profile in blood.
6. To evaluate correlation of genetic markers and EDP1815 treatment outcomes.
7. To evaluate correlation of gut microbiome and EDP1815 treatment outcomes.

3. STUDY VARIABLES

3.1. Efficacy Variable(s)

3.1.1. Primary Efficacy Variable(s)

The primary efficacy endpoint is achievement of an EASI-50 response at Week 16.

3.1.2. Secondary Efficacy Variable(s)

The following secondary endpoints will be evaluated at Weeks 4, 8, 12 and 16 (unless otherwise specified) to evaluate the maximum clinical benefit of EDP1815 in the treatment of atopic dermatitis:

- Percentage of Participants Achieving EASI-50 [Time Frame: Week 4, 8 and 12]
- Percentage of Participants Achieving EASI-75
- Percentage of Participants Achieving EASI-90
- Mean absolute change and percentage change from baseline in EASI Score

- Percentage of Participants Achieving Investigator's Global Assessment (vIGA) of 0 or 1 with a ≥2 Point Improvement from baseline
- Percentage of Participants Achieving vIGA of 0 or 1
- Percentage of Participants Achieving vIGA of 0 [Time Frame: Week 16]
- Mean absolute change and percentage change from baseline in vIGA*BSA
- Mean absolute change and percentage change from baseline in BSA
- Percentage of Participants Achieving BSA-50
- Percentage of Participants Achieving BSA-75
- Percentage of Participants Achieving BSA reduction to 3% BSA or less

- Mean absolute change and percentage change from baseline in SCORing Atopic Dermatitis (SCORAD)
- Percentage of Participants Achieving SCORAD-50
- Percentage of Participants Achieving SCORAD-75

- Mean absolute change and percentage change from baseline in DLQI
- Percentage of Participants achieving a reduction of ≥4 in the DLQI, of those with a score of ≥4 at baseline [Time Frame: Week 16]

- Mean absolute change from baseline in worst Pruritus-NRS
- Percentage of Participants achieving a reduction of ≥2 in the worst Pruritus-NRS, of those with a score of ≥2 at baseline
- Percentage of Participants achieving a reduction of ≥4 in the worst Pruritus-NRS, of those with a score of ≥4 at baseline [Time Frame: Week 16]

- Mean absolute change from baseline in SD-NRS score
- Percentage of Participants achieving a reduction of ≥2 in SD-NRS score, of those with a score of ≥2 at baseline [Time Frame: Week 16]

- Mean absolute change and percentage change from baseline in Patient Oriented Eczema Measure (POEM)
- Percentage of Participants achieving a reduction of ≥4 in the POEM score, of those with a score of ≥4 at baseline [Time Frame: Week 16]

- Number of courses of rescue therapy per Participant
- Number of days of treatment with rescue therapy per Participant
- Proportion of participants not requiring rescue therapy

For secondary estimands, a treatment policy approach will be used with respect to study medication and a composite approach will be used for data collected within 28 days of rescue medication use and withdrawal from the study for reasons related to study treatment.

3.2. Pharmacokinetic and Pharmacodynamic Variable(s)

EDP1815 has no systemic absorption and therefore no systemic exposure. Therefore, no samples for pharmacokinetic analysis will be performed in this study.

3.3. Safety Variables

The severity and frequency of adverse events will be used to evaluate the safety and tolerability of EDP1815. Vitals signs, weight, physical examinations, clinical laboratory tests, ECG and use of concomitant medications will also be used to evaluate the safety and tolerability of EDP1815.

3.4. Exploratory Variables

The following endpoints will be used to evaluate the time to onset of clinical response to EDP1815:

- Time to first achievement of EASI-50
- Time to first achievement of sustained* EASI-50
- Time to first achievement of IGA of 0 or 1 with a 2-point improvement from baseline
- Time to first achievement of a ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline
- Time in days to first sustained** ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline
- Time to first achievement of a ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline
- Time in days to first sustained** ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline
- Time to first achievement of a ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline
- Time in days to first sustained** ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline

* Sustained EASI-50 response is defined as one which is present on at least two consecutive visits.
** Sustained PP-NRS or SD-NRS response is one which is present at all days where the diary is completed in a minimum of a 14-day period

The following endpoints will be used to evaluate other aspects of the efficacy of EDP1815 as a treatment for atopic dermatitis at Weeks 4, 12 and 16 unless otherwise specified:

- Percentage of Participants Achieving Investigator's Global Assessment (vIGA) of 0 or 1 with a ≥2 Point Improvement from screening
- Mean absolute change and percentage change from Screening in EASI Score
- Percentage of Participants developing skin infections requiring topical or systemic antibiotic treatment [Time Frame: Week 16]
- Changes from baseline in SF-12 MCS and PCS scores
- Changes from baseline in HADS anxiety and depression scores
- Changes from baseline in ADCT scores
- Daily changes from baseline in the PP-NRS and SD-NRS [Timescale: Days 2 to 140]

To evaluate the effect of early use of topical corticosteroid rescue therapy on Week 16 responder status, the subgroup of participants with no rescue use at any time before Week 16 will be compared to subgroups of participants with rescue therapy use within only the first 4, 8, 12 and 14 weeks of treatment and to participants with rescue therapy use within the 2 weeks and 4 weeks prior to the Week 16 visit. For these subgroups, the following endpoints will be summarized:

- Percentage of Participants Achieving EASI-50, EASI-75 and EASI-90
- Percentage of Participants Achieving IGA 0 or 1, with and without a 2-point improvement from Baseline
- Percentage of Participants Achieving BSA-50, and BSA-75

The following endpoints will be used to evaluate the effect of EDP1815 treatment on biomarkers in blood at Weeks 2, 16 and 20 (unless otherwise specified):

- Changes from baseline in eosinophils
- Changes from baseline in serum immune protein markers including IgE [Time Frame: Week 16]
- Changes from baseline in immune cell RNA profile

4. STUDY DESIGN

4.1. Study Description

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of EDP1815 as compared to placebo in participants with mild, moderate and severe atopic dermatitis.

This study will consist of 4 cohorts with a possible interim analysis prior to end of recruitment in Cohorts 1, 2 & 3. The purpose of this interim analysis is to check the assumptions around placebo response rate.

Approximately 100 participants will be randomly allocated to each of Cohorts 1, 2, & 3. These cohorts will run concurrently. Within each cohort, participants will then be randomized to treatment in a 3:1 ratio (75 to EDP1815, 25 to placebo). Therefore, across Cohorts 1, 2, & 3, approximately 225 participants will be randomly assigned to receive EDP1815, and 75 participants will be randomized to matching placebo for 16 weeks. Following end-of-treatment assessments, participants may enter a 4-week post-treatment follow-up period or may elect to participate in an Open Label Extension (OLE) protocol for EDP1815, if available.

- **Cohort 1:** $1.6x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 2:** $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 3:** $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 1 capsule of $3.2x10^{11}$ cells twice daily.

Cohort 4 will run after enrollment is completed in Cohorts 1, 2, & 3. Approximately 105 participants in this cohort will be randomized to treatment in a 2:1 ratio (70 to EDP1815, 35 to placebo). Participants will be treated for 16 weeks. Following end-of-treatment assessments, participants may enter a 4-week post-treatment follow-up period or may elect to participate in an Open Label Extension (OLE) protocol for EDP1815, if available.

- **Cohort 4:** $8.0x10^{10}$ total cells of EDP1815 or matching placebo administered as 1 capsule once daily.

4.2. Study Duration per Participant

All cohorts will consist of:

- Up to a 4-week Screening Period
- A 16-week Treatment Period
- A 4-week Post-Treatment Follow-up Period

Total participant duration is up a maximum of 24 weeks from screening to safety follow-up, unless they elect to participate in the OLE protocol, and their maximum participation in this study would be 20 weeks.

The end of the study is defined as the date of the last visit of the last participant (LPLV).

4.3. Planned Number of Participants

This study will be conducted as a multi-center study at approximately 60 centers globally. Approximately 405 total participants will be randomized and treated with EDP1815 or matching placebo.

4.4. Anticipated Regions and Countries

This study may be conducted as a multi-regional study at centers located in North America, Europe and Asia Pacific.

4.5. Schedule of Study Assessments

Table 4-1:Schedule of Assessments

Procedure	Screening	Treatment Period						Week 20 Visit	Early Termination Visit [a]	ET Follow-Up Phone Call [a]	Rescue Therapy Unscheduled Visit [b]
Day	-28 to -1	1	15	29	57	85	113	141			
Week	-4 to -1	0	2	4	8	12	16	20			
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-3	+ 3		+ 3	
Informed consent [c]	X										
Inclusion and exclusion criteria	X	X [d]									
Demography	X										
Medical history and current medical conditions (including smoking status) [e]	X										
Full physical examination [f]	X	X					X		X		
Brief physical examination [f]			X	X	X	X		X			
Height [g]	X										
Weight [g]	X	X		X			X	X	X		
Pregnancy test [h]	X	X		X	X	X	X	X	X		
12-lead ECG [i]	X			X			X	X	X		
Laboratory assessments (hematology including eosinophils, biochemistry, urinalysis)	X	X [d]	X	X	X	X	X	X	X		
OPTIONAL Biomarker (blood) collection: DNA Collection		X									
Biomarker (blood) collection: Inflammation immune surveillance in circulation		X	X				X	X	X		

Procedure	Screening	Treatment Period						Week 20 Visit	Early Termination Visit [a]	ET Follow-Up Phone Call [a]	Rescue Therapy Unscheduled Visit [b]
Day	-28 to -1	1	15	29	57	85	113	141			
Week	-4 to -1	0	2	4	8	12	16	20			
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-3	+ 3		+ 3	
Biomarker (blood) collection: Immune protein markers		X					X		X		
Biomarker (fecal) collection: Microbiome sample**		X									
Vital signs [j]	X	X	X	X	X	X	X	X	X		
Randomization		X [k]									
Dosing [l]		X									
Dispense IMP		X	X	X	X						
IMP accountability / Collect empty wallets/cartons				X		X	X		X		
Digital photography [m]		X		X		X	X	X	X		
vIGA [n]	X	X	X	X	X	X	X	X	X		X
BSA involvement (%) [n]	X	X	X	X	X	X	X	X	X		X
EASI [n]	X	X	X	X	X	X	X	X	X		X
SCORAD [n]		X	X	X	X	X	X	X	X		
POEM		X	X	X	X	X	X	X	X		
DLQI		X	X	X	X	X	X	X	X		
PP-NRS[o]	X	→							X		
SD-NRS[p]	X	→							X		
SF-12		X		X		X	X	X	X		

Procedure	Screening	Treatment Period						Week 20 Visit	Early Termination Visit [a]	ET Follow-Up Phone Call [a]	Rescue Therapy Unscheduled Visit [b]
Day	-28 to -1	1	15	29	57	85	113	141			
Week	-4 to -1	0	2	4	8	12	16	20			
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-3	+ 3		+ 3	
HADS		X		X		X	X	X	X		
ADCT		X		X		X	X	X	X		
AE/SAE review [q]	X	→									
Concomitant medication review	X	→									
Participant diary [r]		X	X	X	X	X	X	X	X		
Emollient check [s]		X	X	X	X	X	X	X	X		

[a] Participants who withdraw from the study early will have an Early Termination Visit and complete the assessments specified for Early Termination Visit. If due to treatment failure, this visit should be arranged within 72 hours of the start of any AD therapy, when possible. The participant will also be asked to have a final telephone call 28 days (+3 days) after taking their last dose of IMP for safety assessments. The date of this telephone call will be considered the end of study date for these participants.

[b] Rescue Therapy Unscheduled Visit to be scheduled when rescue therapy is given outside of a scheduled visit. This visit shall be repeated each time a course of rescue therapy is considered/requested.

[c] Informed consent (and re-consent, as applicable) must be obtained by the Principal Investigator or a licensed physician investigator (i.e., Sub-Investigator) per Good Clinical Practice (GCP) and local guidelines.

[d] Inclusion/exclusion criteria to be assessed before first dose of IMP. Screening laboratory results will be used to confirm eligibility at Day 1 Visit.

[e] Smoking status to include whether current-smoker, ex-smoker or never smoker, and to quantify current usage and total pack-year history.

[f] A physical examination (PE) will be conducted at every visit. At Screening, Day 1 and Week 16 a full PE will be performed, and the following body systems will be evaluated: general appearance, cardiovascular, respiratory, gastrointestinal, musculoskeletal, central nervous system, lymph nodes and skin. At Weeks 2, 4, 8 12 and 20, a brief PE will be performed, and the following body systems will be evaluated: general appearance, cardiovascular, respiratory, gastrointestinal and skin.

[g] BMI will be calculated from the height (collected at Screening) and weight.

[h] Women of child-bearing potential only. Serum HCG at Screening. Pregnancy testing (urine) will be performed at the visits indicated and if a menstrual cycle is missed or if pregnancy is otherwise suspected.

[i] A single ECG tracing is to be obtained on the day of the visit approximately 5 minutes after the participant has rested. If, in the opinion of the Investigator, there appear to be clinically significant findings, repeat tracings should be obtained, as necessary.

[j] Blood pressure, heart rate, respiratory rate, and temperature will be measured after approximately 5 minutes after the participant has rested.

[k] Participant to be randomized after all Day 1 activities are completed and patient is still eligible to participate in the study.

[l] The first IMP dose will be given at the Day 1 visit after all procedures are completed following randomization. Subsequent doses are taken daily in the morning at approximately the same time ±2 hours where possible. On study visit days, dosing may occur at home prior to the study visit, even if dosing falls outside the dosing window. Participants should refrain from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing.

[m] Digital photographs should be taken of the upper and lower body (upper & lower anterior and upper & lower posterior) as half body shots. Additional close-up photographs of up to six specific body areas (i.e., limbs, trunk and back) will also be taken. The same sites photographed at Day 1 should be followed throughout the study for each participant.

[n] AD Investigator rating scales. Participants will be asked to withhold all emollients, sunscreens, or moisturizers on the day of these study visits until all study assessments are completed.

[o] The Pruritus-NRS (worst itch) will be asked daily from the Screening Visit to the Week 20 Visit via a participant diary.

[p] The Sleep Disturbance-NRS (SD-NRS) will be asked daily starting at the Screening Visit to the Week 20 Visit via a participant diary.

[q] Adverse Events (AE) and Serious Adverse Events (SAE) will be captured from the time the participant signs the informed consent.

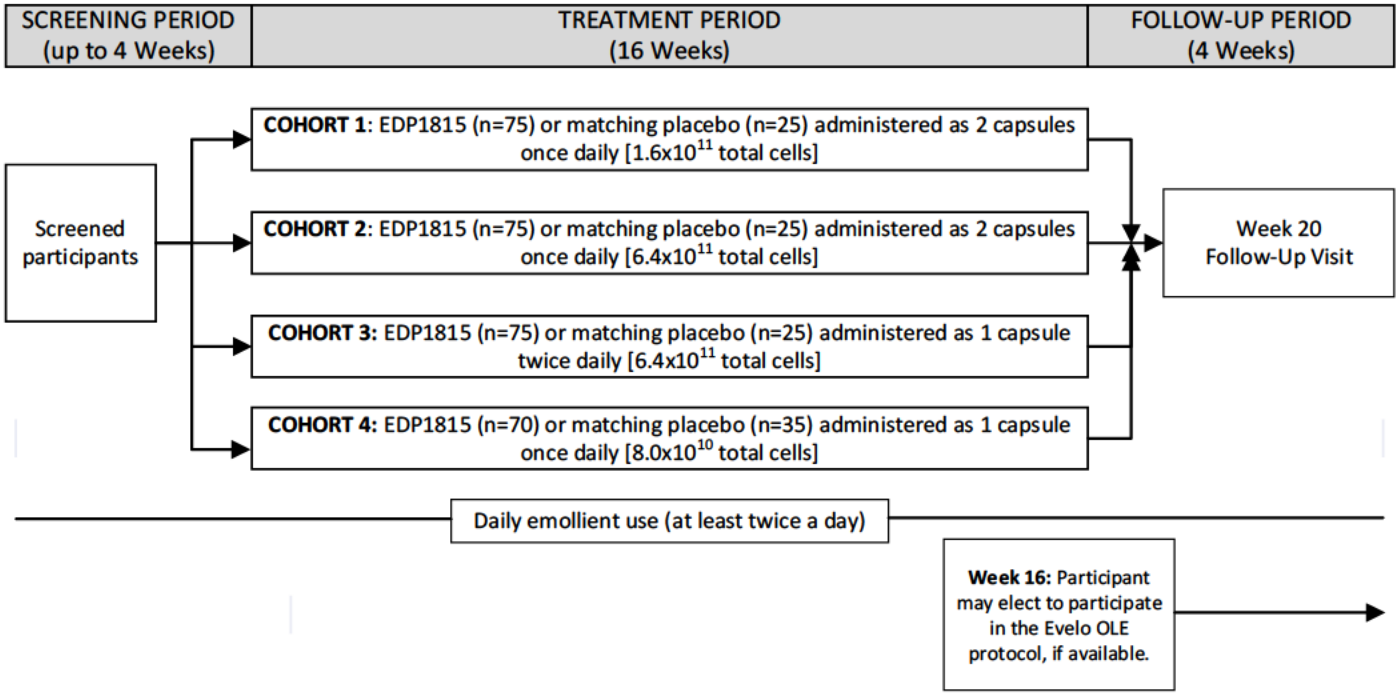
[r] Study staff will review the patient diary with participants at each visit. Diaries will be reviewed for completeness and accuracy, and participants will be coached as needed on compliance with the protocol.

[s] Patients will be asked if they have enough emollient to last them until the next study visit.

** A fecal sample is not required for any participant that enrolls under Protocol Version 5.0.

4.6. Schematic Study Diagram

Figure 4-1: Schematic Diagram



4.7. Rationale for study design and selection of dose

4.7.1. Placebo Rationale

EDP1815-207 will utilize a matching placebo control in each cohort in order to fulfill the double-blind design of the study, so that neither the investigator nor subject has knowledge of the treatment being administered. The purpose of this study design is to control for the placebo effect, control for variables caused by knowledge of treatment assignment, control for other factors that can influence study outcomes, and finally to allow for a more complete understanding of the risk-benefit profile of the active study drug. A position statement from the International Eczema Council (Leshem, et al., 2019) has given clear guidance on the design of studies in atopic dermatitis, including supporting and giving a scientific rationale for the use of placebo-control in studies in this condition. Placebo-controlled studies are the recommended standard. In addition, in this study, we are minimizing the proportion of placebo subjects by using a 3:1 randomization ratio (Cohorts 1-3) between active and placebo, and then pooling the placebo subjects together for comparison. In Cohort 4, a 2:1 randomization ratio will be used together with a strategy that allows for a proportion of placebo participants from Cohorts 1-3 to be borrowed using a matching algorithm to increase power while also minimizing the proportion of placebo participants.

4.7.2. Dose Rationale

The study is designed to evaluate the efficacy of EDP1815 in the treatment of atopic dermatitis at three different doses across two regimens, $8.0x10^{10}$ total cells QD, $1.6x\ 10^{11}$ total cells QD, $3.2x10^{11}$ total cells BID and $6.4x10^{11}$ total cells QD.

The pharmacological site of action of EDP1815 is within the epithelium of the small intestine where EDP1815 interacts with immune and epithelial cells. These interactions modify the systemic immune system and promote inflammation resolution throughout the body. The preclinical and clinical data generated to date suggest this is a broad effect working across Th1, Th2 and Th17 pathologies. As the intent is to generate a maximal inflammation-resolving phenotype regardless of inflammation pathology, the dose response is expected to be common across indications, and therefore we aim to cross compare to previous studies to support this hypothesis. A full dose-ranging study is currently being carried out in a phase 2 study (EDP-1815-201) in psoriasis patients.

Evelo's Phase 1 Study EDP1815-101 evaluated EDP1815 for the treatment of atopic dermatitis with an oral dose of $8.0x10^{11}$ cells delivered as ten capsules once a day for 8 weeks. This dose was safe and well tolerated and clinical benefit was observed with an improvement of 50-65% over placebo by Week 8 in EASI, SCORAD, and vIGA*BSA endpoints. In addition, doses of $1.6x10^{11}$ and $8.0x10^{11}$ total cells given for 28 days have been investigated in this study for the treatment of psoriasis. Similar clinical benefit was observed at both dose levels. A Phase 2 dose ranging study in psoriasis (EDP1815-201) was conducted in approximately 225 participants for 16 weeks, at doses of $8.0x10^{10}$, $3.2x10^{11}$, and $8.0x10^{11}$ total cells. No evidence of dose response was seen in this study. Further information on these studies is detailed in the EDP1815 Investigator's Brochure (IB).

The doses selected for evaluation in EDP1815-207 represent commercially acceptable dosing regimens in terms of capsule load and frequency for patients. The doses of $8.0x10^{10}$ total cells and

$1.6x10^{11}$ total cells are comparable with data being generated in the lower dose cohorts of EDP1815-201, whilst the dose of $6.4x10^{11}$ total cells approximates to that administered in EDP1815-101, cohort 7. This latter total daily dose is being tested as both a once daily and twice daily regimen, to explore whether this leads to a change in the efficacy profile of EDP1815 in atopic dermatitis.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

Participants with a confirmed diagnosis of mild, moderate or severe atopic dermatitis will be treated in this study only if they meet all inclusion and no exclusion criteria during screening. Any participant who signs the informed consent form will be considered enrolled in the study. Study screening procedures will begin after participants sign the informed consent.

5.1. Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements.

2. Males or females aged ≥ 18 and ≤ 75 years old at the time of informed consent.

3. A diagnosis of atopic dermatitis (AD) meeting Hanifin and Rajka criteria for AD at screening (Appendix 14.1) with patient- or clinician- reported disease duration of at least 6 months.

4. Have severity of atopic dermatitis meeting the below criteria at both Screening and Day 1:
   i. An IGA of 2, 3 or 4 on the vIGA scale, and;
   ii. A BSA of ≥5%, and;
   iii. An EASI score of ≥6.

   A cap will be set for each of the three IGA severity grades. When this cap is reached, Sponsor will notify sites that participants with severity score at Screening and/or Day 1 matching the closed stratum should be considered ineligible according to Inclusion Criterion 4i.

5. All participants must agree to use a bland additive-free, sodium lauryl sulfate (SLS)-free, and fragrance-free emollient cream, gel or ointment twice daily (or more, as needed) for at least 14 consecutive days immediately prior to randomization and must continue this treatment twice daily throughout the trial. See **Section 6.9.1.1. Background Therapy**.

6. Meet the following contraception criteria:
   i. Male participants:
      i. A male participant must agree to use contraception as detailed in Appendix 14.3 of this protocol during their participation in this study and for a period of 90 days after the last dose and refrain from donating sperm during this period.
   ii. Female participants:
      i. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
         1. Not a WOCBP as defined in Appendix 14.3 or
         2. A WOCBP who agrees to follow the contraceptive guidance in Appendix 14.3 during their participation in this study, 28 days prior to the first dose and for at least 1 complete menstrual cycle (≥30 days) after the last dose.

   Agrees to not increase their usual sun exposure significantly during the study.

5.2. Exclusion criteria

Participants are not permitted to enroll in the study if any of the following criteria is met:

1. Atopic dermatitis limited to the hands and/or feet and/or scalp.

2. Have been in a clinical trial for EDP1815 prior to signing of ICF.

3. History of active skin infection within 14 days prior to randomization.

4. Evidence of dermatologic conditions that may, in the opinion of the investigator, interfere with AD evaluation or the assessment of treatment response.

5. Use of phototherapy or tanning beds; systemic medications/treatments that could affect AD or its symptoms including immunosuppressive therapy (e.g., oral or injectable corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, JAK inhibitors, tacrolimus, and/or leukotriene inhibitor) within 4 weeks of randomization.

6. Previously received any biologic agent for AD and either was:
    a. Unresponsive to biologic agent, or
    b. Responsive to biologic agent and received this therapy within 3 months or 5 half-lives prior to randomization, whichever is longer.

7. Treatment with topical agents that could affect atopic dermatitis, including topical corticosteroids, topical calcineurin inhibitors (e.g., tacrolimus or pimecrolimus), or topical PDE-4 inhibitor (e.g., crisaborole) within 14 days prior to randomization.

8. Received any investigational or licensed biologic agent for conditions other than AD:
    a. Any cell-depleting agent, including rituximab, within 6 months prior to randomization, or until lymphocyte cell counts return to normal, whichever is longer.
    b. Any other biologic agent, within 3 months or 5 half-lives prior to randomization, whichever is longer.

9. Gastrointestinal tract disease (e.g., short-bowel syndrome, diarrhea-predominant irritable bowel syndrome) that could interfere with GI delivery and transit time.

10. Active inflammatory bowel disease.

11. Ongoing acute or chronic infectious disease. Patients with hepatitis B, hepatitis C, and HIV may be enrolled provided that the disease is adequately controlled and/or is in remission.

12. Has received live or live-attenuated vaccination within 6 weeks prior to Screening or intends to have such a vaccination during the study. Non-live and non-replicating vaccines are permitted.

13. Clinically significant abnormalities in screening laboratory values that in the opinion of the Investigator would make a participant unsuitable for inclusion in the study. One retest is permitted within the 28-day screening window.

14. Screening Labs: For women, serum creatinine ≥125 µmol/L (1.414 mg/dL); for men, serum creatinine ≥135 µmol/L (1.527 mg/dL).

15. Screening Labs: ALT or AST >2 × ULN.

16. History of clinically significant acute cardiac or cerebrovascular event within 6 months of signing ICF (includes stroke, transient ischemic attack, and coronary heart disease [angina pectoris, myocardial infarction, heart failure, revascularization procedures]).

17. History of active substance (drug and/or alcohol) abuse within the prior 12 months. This does not include the current or prior use of cannabis.

18. In the opinion of the Investigator, evidence of clinically important cardiac conduction abnormalities as judged by the screening ECG.

19. Hypersensitivity to *P histicola* or to any of the excipients.

20. Active mental or psychiatric disorder, which, in the opinion of the Investigator or Sponsor, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study.

21. Recent major surgery within 3 months of signing the ICF, or major surgery planned during the study.

22. Malignancy within 5 years of signing the ICF, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

23. Treatment with another investigational drug or device within 3 months or 5 half-lives of investigational agent prior to randomization, whichever is longer.

24. Treatment with supplements containing high doses of probiotics and prebiotics as usually found in capsules/tablets/powders, within 14 days prior to randomization and throughout the study period. Note that probiotic and prebiotic foods that contain low doses are allowed (e.g., yoghurt, kefir, kombucha).

25. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.

26. Have any serious conditions that would be anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma).

27. Have any other conditions, which, in the opinion of the Investigator or Sponsor, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study due to failure to meet eligibility criteria or failing to randomize for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent, demography, screen failure details, eligibility criteria, and any AEs and SAEs.

5.3.3. Rescreening

Participants who fail to satisfy inclusion and exclusion criteria at Screening may be rescreened one additional time with the agreement of the Medical Monitor before re-screening.

A participant that is re-screened will be assigned a new participant identifier (ID). Additional information on rescreening will be provided in the appropriate specific user manual.

5.4. Discontinuation from Treatment and/or Withdrawal

Participants may discontinue from treatment and withdraw their participation from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing treatment and withdrawing from the study will be recorded in the source files and on the eCRF.

Interruption of treatment is defined as a temporary stopping of IMP that resumes during the treatment period, due to an AE or any other reason. The maximum permitted interruption at one time is 7 days and the participants should not interrupt IMP for more than 14 days in total.

Early discontinuation of treatment is defined as permanent stopping of IMP before the Week 16 visit. Investigators will strive to ensure that a participant who has interrupted treatment for a particular reason will not discontinue IMP unless discontinuation is medically imperative in the Investigator's judgment. However, a dose interruption of more than 7 days or multiple dose interruptions totaling more than 14 days will result in mandatory discontinuation of IMP and early termination of the participant.

Early withdrawal from the study is defined as failing to complete the 16-week treatment and the 4-week follow-up period unless the participant transitions to the Open Label Extension (OLE) Protocol at Week 16.

A participant will discontinue IMP and be withdrawn from the study for any of the following reasons:

1. The participant experiences treatment failure, demonstrated by the participant commencing phototherapy, an oral agent, biological, or intermediate or high-potency topical therapy other than those permitted as rescue therapy.

2. The participant has a serious or intolerable AE that in the Investigator's opinion requires discontinuation from IMP and withdrawal from the study.

   NB: Dosing may be interrupted at the Investigator's discretion due to AE or intercurrent illness for a period of up to 7 days, following which the participant may resume treatment if the Investigator considers it safe to do so. The participant should discontinue treatment permanently if the same AE which caused dose interruption occurs a second time requiring another dose interruption and is believed to be related to treatment.

3. The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal.

4. The participant is lost to follow-up.

5. Other reasons (e.g., pregnancy, development of contraindications to use of IMP).

6. The participant withdraws consent, or the Investigator or Sponsor decides to discontinue the participant's participation in the study.

A participant may discontinue IMP and be withdrawn from the study for any of the following reasons:

1. The participant is noncompliant with the protocol.

2. The participant has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.

3. If the participant is required to start therapy for a concurrent condition that may affect the study endpoints, e.g., a disease modifying agent for asthma.

Investigators should contact the Medical Monitor, whenever possible, to discuss the treatment discontinuation and withdrawal of a participant in advance of this decision.

Investigators should attempt to obtain information on participants in the case of treatment discontinuation and withdrawal. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The CRF must document the primary reason for treatment discontinuation and withdrawal.

5.4.1. Withdrawal from the Study

Participants may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. The Investigator will also withdraw a participant if Evelo terminates the study.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the source and eCRF.

The participant randomization number accounts for an expected drop-out rate of approximately 20%.

The drop-out rate within each treatment group will be estimated during the interim analysis. Should 1 or more treatment groups be found to have a drop-out rate of 25% or more, additional participants will be randomized.

5.4.2. Lost to Follow-Up

A participant will be considered lost to follow-up if s/he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a written message to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the eCRF (date and summary of the phone call and copy of the written message in the source documents).

If the participant continues to be unreachable, s/he will be considered to have withdrawn from the study.

6. STUDY TREATMENT(S)

6.1. Investigational Medicinal Product(s)

Investigational Medicinal Product (IMP) is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

All IMP in this study will be administered orally. EDP1815 will be supplied as capsules that are enteric-coated to release the contents upon gastric emptying. EDP1815 enteric-coated capsules contain lyophilized *Prevotella histicola*, mannitol, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, methacrylic acid-ethyl acrylate copolymer, talc, triethyl citrate, titanium dioxide, and iron oxide.

EDP1815 capsules will be manufactured in the following dose strengths and associated enteric coating thickness (EC). The thickness of the capsule enteric coating for Cohort 4 is thinner (EC2) than the capsule enteric coating for Cohorts 1, 2, & 3 (EC1):

Cohort 1: $8.0x10^{10}$ total cells per capsule (EC1)
Cohort 2 & 3: $3.2x10^{11}$ total cells per capsule (EC1)
Cohort 4: $8.0x10^{10}$ total cells per capsule (EC2)

The drug substance used in Cohorts 1 and the 4 is manufactured by a different process than used in Cohorts 2 and 3. The drug substance in Cohorts 2 and 3 was manufactured using an optimized process to yield a higher concentration of microbe per capsule. It has been demonstrated to be similar to the drug substance in DTH mouse and healthy-volunteer human models. All IMP, regardless of manufacturing processes, is identical in appearance. Further information is detailed in the EDP1815 IB. The drug product is manufactured by [redacted].

The matching placebo is identical in appearance but does not contain *P histicola* or any other bacteria. The coated placebo capsules are composed of microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, methacrylic acid-ethyl acrylate copolymer, talc, triethyl citrate, titanium dioxide, and iron oxide. The matching placebo capsules are manufactured by [redacted]

6.2. Investigational Medicinal Product(s) to be Administered

The study IMP (EDP1815 or placebo) will be administered as capsules for 16 weeks in total.

Study IMP is to be taken with water at approximately the same times each day (±2 hours, whenever possible). With twice daily dosing, administration should be in the morning and evening, with the doses separated by approximately 12 hours (±2 hours, whenever possible).

Participants should refrain from consuming acidic drinks (such as cola/soda, coffee, sports and energy drinks, flavored waters and citrus juices) 1 hour either side of dosing and from eating 2 hours before and 1 hour after dosing.

Table 6-1: IMP to be Administered

Cohort	Formulation	Capsule Number and Frequency	Total Daily Dose / Total Daily Cell Count	Route	Storage Conditions (per label)
1	$8.0x10^{10}$ cells/enteric coated capsule (EC1)	2 capsules, once daily	$1.6x10^{11}$ cells	Oral	Store 2 to 8°C
2	$3.2x10^{11}$ cells/enteric coated capsule (EC1)	2 capsules, once daily	$6.4x10^{11}$ cells	Oral	Store 2 to 8°C
3	$3.2x10^{11}$ cells/enteric coated capsule (EC1)	1 capsule, twice daily	$6.4 x10^{11}$ cells	Oral	Store 2 to 8°C
4	$8.0x10^{10}$ cells/enteric coated capsule (EC2)	1 capsule, once daily	$8.0x10^{10}$ cells	Oral	Store 2 to 8°C

6.3. Packaging

All IMP will be prepared in blister wallets of 10 capsules. Three blister wallets will be packaged in a carton. Cartons will be dispensed per the schedule of assessments (SOA). Multiple packs will be assigned and dispensed for each participant to cover the entire 16-week treatment period.

6.4. Labeling

Cartons and study wallets will be labelled and released in accordance with International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any country required statements. Supplies will be identified by the blinded batch number, expiry date and a unique numeric code which will be used by the Interactive Response Technology (IRT) system to identify content and allocate cartons to study participants.

6.5. Handling and Storage Requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (e.g., room, refrigeration unit) or by completion of a daily temperature log in accordance with local requirements, showing actual and minimum/maximum temperatures reached over the last 24-hour time period.

In case a temperature excursion is noted, it must be immediately reported as per instructions contained in the EDP1815 IMP Handling Manual.

The Investigator (or designee) will instruct the participant to store the IMP following the instructions on the label.

6.6. IMP Accountability

An Interactive Response Technology (IRT) system will be used to record IMP dispensing and return information on a by-participant basis during the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded. All supplies and pharmacy documentation must be made available throughout the study for the Sponsor (or designee) to review.

Participants will utilize an electronic diary (eDiary) to record their IMP intake on a daily basis (**Section 6.6.1 eDiary**).

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for IMP accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

All used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and returned to the Sponsor or designee or it may be destroyed at the site according to applicable laws and regulations, and Sponsor SOPs, if applicable. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.6.1. eDiary

The primary purpose of the diary is to enhance participant compliance with the protocol. All participants will be provided with a paper participant diary at the Screening Visit to record their emollient use and daily PP-NRS and SD-NRS scores prior to the Day 1 Visit. The participants will then utilize an electronic diary (eDiary) commencing upon completion of the Day 1 Visit through the Week 20 Follow-Up Visit. The eDiary will be an application (app) that will be downloaded to the participant's mobile smartphone, and for those participants that do not have a mobile smartphone or do not wish to download an app to their phone, they will receive an eDiary device specifically designated for the purpose of collecting information as described below. Participants will be asked to capture the following information in their eDiary:

- Study IMP
  - Confirmation of dosing
  - Date and time of dosing
  - Number of capsules taken, with reasons not taken, if applicable.
- Background Therapy (Emollient(s))
  - Frequency of usage (number of times a day)
- Rescue Therapy Usage
  - Confirmation of usage
- Daily Peak Pruritus Numerical Rating Scale (PP-NRS)

  - Evaluation of worst itch over previous 24-hour period
- Daily Sleep Disturbance Numerical Rating Scale (SD-NRS)
  - Evaluation of worst sleep over previous 24-hour period

Study staff will review the eDiary entries with participants at each visit. eDiaries will be reviewed for completeness and accuracy, and participants will be coached as needed on compliance with the protocol.

At the Week 20 Follow-Up Visit, the study staff will assist the participants to uninstall the eDiary application on their mobile smartphone devices and/or collect any eDiary devices that were distributed to the participants.

6.7. Drug Compliance

Participants will use the eDiary to capture compliance with their study IMP. At specified visits per the Schedule of Activities (SOA), the study site staff will check numbers of used/unused capsules against diary entries and remind the participant of the need to self-administer the capsules as directed, and to store the IMP according to label instructions.

Prior to the specified study visits per the SOA, study site staff will call participants to remind them to bring all empty IMP wallets and cartons in the original containers to the study site for their visit. If a participant is found to be persistently noncompliant, the Sponsor, in conjunction with the Investigator, will decide as to whether the participant should be withdrawn from the study.

6.8. Dose Modification

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency may be allowed for safety or tolerability after consultation with the Medical Monitor. The maximum permitted interruption at one time is 7 days and the participants should not interrupt IMP for more than 14 days in total.

6.9. Concomitant Medications and Treatments

Throughout the study, the participant may be prescribed concomitant medications or treatments deemed necessary to provide adequate supportive care at the discretion of the Investigator provided that the medications are licensed. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

All concomitant medications and/or treatments received by a participant should be recorded on the appropriate source document and eCRF with the following minimum requirements:

- Drug trade name
- Total daily dose
- Dates of administration
- Reason for use (indication)
- Dosage information (including dose and frequency)

This will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter (OTC) medications, and vaccines. Any changes in concomitant medications also will be recorded

in the participant's eCRF. The participant's dosing diary may contain information relevant to the documentation of changes in concomitant medication.

6.9.1. Permitted Concomitant Medications and Treatments

The following concomitant medications are permitted for use during the study:

- Concomitant medications for conditions other than AD may continue throughout the trial, if not meeting any exclusion criteria, and should continue without change in dosage or formulation whenever possible.
- New therapy/treatments, not expected to have any impact on AD, but deemed necessary for the welfare of the participant during the study, are permitted. If there is doubt about their impact on AD or ability to continue in the study, then this should be discussed with the Medical Monitor.
- Topical and oral antibiotics (For suspected skin infection, see **Section 6.9.1.2 Rescue Therapy)**
- All participants must use an emollient twice daily for at least 14 consecutive days prior to Day 1 and throughout the study (**Section 6.9.1.1 Background Therapy)**.
- Topical and oral antibiotics, antiviral, or antifungal therapy.
- Oral antihistamines.
- Nasal, inhaled and ophthalmic corticosteroids.
- Non-replicating / Non-live vaccines (**Section 6.9.3 Immunizations)**.

6.9.1.1. Background Therapy

All participants must use an emollient twice daily to all body areas for at least 14 consecutive days immediately prior to randomization. This must be a bland emollient which is additive-free, SLS-free, and fragrance-free and may be in cream, gel or ointment formulation. Whenever possible, the same brand and formulation of emollient should be used throughout the study by a participant. Participants are not allowed to use emollients containing additives (e.g., urea, ceramide, nicotinamide). Participants should continue this background emollient treatment twice daily until the Week 20 Follow-up Visit but if a daily dose is missed, this will not be a protocol deviation. On the day of the study visits, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed.

Participants will be considered to have acceptable compliance with respect to emollient use if they administer at least 75% of the expected applications during the study. Participants need to meet this criterion within the 14 days prior to randomization in order to be randomized (i.e., 21 applications of emollient out of the previous 28 applications (14 days) immediately prior to Day 1). Otherwise, participants may be considered for re-screening.

If a participant is found to be persistently noncompliant, the Sponsor, in conjunction with the Investigator, will decide as to whether the participant should be withdrawn from the study.

Background therapy between Screening and Randomization will be recorded via a paper diary. Participants will record their background therapy via the participant eDiary from Day 1 to the Week 20 Follow-Up Visit (**Section 6.6.1 eDiary**).

Please contact the Medical Monitor to discuss any questions on the use of background therapies.

6.9.1.2. Rescue Therapy

If required, Investigators may prescribe / recommend prescription of rescue therapy for participants experiencing unacceptable worsening of atopic dermatitis. Additionally, individuals with uncontrolled atopic dermatitis could be at risk for a secondary skin infection. These participants may be prescribed an antimicrobial therapy to treat the infection as detailed below. Rescue therapy use is allowed throughout the entire study. There is no limit on the number of times that topical rescue therapy can be prescribed, although Investigators and participants may wish to consider whether the study is suitable for them if repeated courses are required.

Rescue therapy, including antimicrobial rescue therapy, should be prescribed as detailed below, and any specific deviations should first be discussed with the Medical Monitor. Participants rescued by such topical therapy will continue to take IMP and use of rescue therapy will be documented in the participant eDiary (**Section 6.6.1 eDiary**). Of note, Investigators should make every attempt to conduct the following assessments immediately prior to administering any rescue therapy, by use of an unscheduled visit, if needed:

- EASI
- vIGA
- PP-NRS
- AEs
- Concomitant Medications

For non-sensitive body sites:

- Moderate potency (grade IV and V – Appendix 14.2) topical corticosteroids, twice daily for up to 7 days

For sensitive sites e.g., head and neck:

- Topical tacrolimus (0.1%), topical pimecrolimus (1%) or grade VII topical corticosteroid, twice daily for up to 7 days

If topical rescue therapy fails to control symptoms adequately, then the participant should be considered for alternative systemic therapy or phototherapy by the Investigator/their practitioner, at which point they will be classified as a treatment failure and IMP will be discontinued.

For possible skin infection:

- Topical:
  - Appropriate courses of topical antimicrobial therapies, such as fucidic acid cream (e.g., Fucidin), are acceptable for use for skin infections, as required
  - If requiring concomitant moderate potency steroid therapy, fucidic acid with betamethasone 0.1% (as the valerate ester), (e.g., Fucibet cream) twice daily for up to 7 days
- Oral:
  - Appropriate course(s) of oral antibiotic(s) may be prescribed as per clinical need

6.9.2. Prohibited Concomitant Medications and Treatments

6.9.2.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Live (attenuated) vaccinations: not permitted at any point during the study (**Section 6.9.3 Immunizations).**

6.9.2.2. Discontinuation of Prohibited Concomitant Medications

Use of any of the following concomitant medications during the study require the concomitant medication to be immediately discontinued where possible. If the prohibited medication cannot be discontinued for any reason, then the IMP should be discontinued:

- Emollients containing additives including SLS
- Topical Corticosteroids or Topical Calcineurin Inhibitors (unless used as Rescue Therapy, **Section 6.9.1.2 Rescue Therapy**)
- Topical PDE-4 Inhibitors
- Bleach baths
- Tanning beds
- Leukotriene Receptor Antagonists
- Allergen Immunotherapy

6.9.2.3. Prohibited Concomitant Medications Requiring IMP Discontinuation

Introduction of any of the following concomitant medications during the study will be classified as a treatment failure and require IMP discontinuation:

- Phototherapy treatment
- Systemic treatments that may lead to clinical improvements in atopic dermatitis, e.g., oral or injectable corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, JAK-inhibitors, biologic therapy, and other systemic immunosuppressive therapy (note single dose intra-articular or intra-lesional corticosteroid therapy is permitted).

6.9.3. Immunizations

Non-replicating / Non-live vaccines are permitted during the study. This includes all SARS-CoV-2 (COVID) non-live vaccines and non-replicating vaccines. However, the first dose of IMP should not be taken within a 7-day window of administration of the vaccine.

Live (attenuated) vaccinations are not permitted at any point during the study. This includes vaccines for measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, and influenza (intranasal). The non-intranasal seasonal flu vaccine is permitted, as is the recombinant zoster vaccine (non-live).

6.10. Blinding

Cohort assignments will not be blinded however, assignment to IMP within a cohort will be blinded. All IMP within a cohort (EDP1815 and matching placebo) will be supplied in identical packaging, color, smell, and appearance to enable double-blinded conditions that ensure all Investigators, study site staff, participants, and clinical monitors will remain blinded throughout the study. The IRT system will assign IMP to participants at the time of randomization. Only

personnel supporting the IRT system, the independent randomization team, and clinical supplies will be unblinded and will have access to treatment assignments; all other parties involved in the study will be fully blinded.

For the interim analysis just before the end of recruitment to Cohorts 1, 2 & 3, unblinded aggregate results will be produced by an unblinded team (external to Evelo) and reviewed by senior Evelo personnel who are not participating in study conduct to allow decision making on increasing the sample size. These will not be shared with any study site staff, participants, or any members of the study team who will be involved in the collection, review or analysis of individual study data.

6.10.1. Breaking the Blind

A participant's treatment assignment will not be unblinded for the Investigator or study site staff until end of study unless medical treatment of the participant depends on knowing the study treatment the participant received. In the rare event that unblinding is needed because of a medical emergency, the Investigator may unblind an individual participant's treatment allocation through the IRT. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. If a participant's study treatment assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. Reasons for treatment unblinding must be clearly explained and justified in the source and eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Participants who are unblinded will be allowed to continue their participation in the study; however, any data collected after the unblinding occurred may be excluded from one or more of the defined data point sets.

The Clinical Safety Team at [redacted] will be unblinded to study treatment to facilitate appropriate identification and reporting of SUSARs to Competent Authorities and the relevant IECs/IRBs.

6.11. Randomization

An IRT will be used for assigning eligible participants to a cohort (as applicable) based on a predetermined production randomization and/or packaging schedule. The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for participant kits of IMP, as appropriate, according to the visit schedule.

To randomize a participant, the Investigator or designee will contact the IRT and provide brief details about the participant to be randomized. The IRT will assign a participant randomization number. The IRT will allocate kit numbers to the participant based on the participant number during the course of the study. The kit number may be incorporated into the CRF.

The randomization schedule will be stratified by vIGA at Day 1 to ensure that the cohorts and treatment groups within Cohorts 1, 2, and 3 are balanced with respect to disease severity. The randomization schedule for Cohort 4 will also be stratified by vIGA at Day 1. In order to match as

closely as possible the severity of Cohorts 1, 2 & 3. Cohort 4 may also limit the numbers of participants recruited to each strata to match the proportions of each vIGA strata in Cohorts 1, 2 & 3.

7. STUDY PROCEDURES BY VISIT

No study procedures should be performed prior to the signing of the informed consent form (ICF).

Visit windows are consecutive calendar days and the target visit dates are calculated from the Day 1 visit.

The Schedule of Activity (SOA) is presented in **Table 4-1**. An overview of each of the study assessments is presented in the subsections below. If a visit is not completed per protocol, it will be considered a missed visit. The site should still contact the participant by telephone to ensure that there have not been any adverse reactions.

7.1. Screening Visit

At the time of Screening, each site will sequentially assign a unique identifier to each participant which will be used for the duration of the study.

The following procedures will be performed at the Screening Visit to determine the participant's eligibility for the study:

- Obtain written informed consent from participant
- Assess inclusion and exclusion criteria
- Collect demographics including year of birth, age, gender, race, and ethnicity.
- Obtain medical history including onset year of AD and the participant's smoking status
- Perform full physical examination
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) including height and weight
- Perform 12-lead electrocardiogram (ECG)
- Collect blood for screening labs
- Collect urine for screening urinalysis
- Perform serum pregnancy test for women of child-bearing potential (WOCBP)
- Determine the Investigator's Global Assessment (vIGA) Score
- Perform EASI rating scale and determine BSA involvement (%)
- Review and document concomitant medications and therapies
- Assess and document adverse events (AEs) that occur after participant signs informed consent form (ICF)
- After the participant has completed all screening activities, provide them the Patient Skin Care Instructions for emollient, as well as paper diaries for recording emollient use and the PP-NRS and SD-NRS scores.

7.2. Day 1 Visit

All participants must use an emollient twice daily for at least 14 consecutive days prior to randomization with a minimum compliance of 75% total applications (minimum of 21 out of the 28 applications in the 14 days prior to day 1). On the day of the Day 1 Visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed (**Section 6.9.1.1 Background Therapy**).

The Day 1 Visit will take place within 28 days of the Screening Visit. The following procedures will be performed:

- Review inclusion and exclusion criteria
- Perform full physical examination
- Measure vital signs including weight
- Collect blood for safety labs as well as serum immune protein markers and inflammatory markers
- Collect urine for urinalysis
- Perform urine pregnancy test for WOCBP
- Take digital photographs of the upper and lower body (anterior and posterior) as half body shots. Additional photographs of up to six specific body areas, i.e., limbs, trunk and back (excluding scalp, genitals and any identifying features) may also be taken.
- Perform AD rating scales - vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – HADS, POEM, DLQI, ADCT, and SF-12
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- OPTIONAL: If participant consented to genetic testing, collect appropriate blood sample

Randomization Procedures

- Randomize the participant in IRT after all Day 1 activities are completed and the participant is still deemed eligible to participate
- Administer the first dose of IMP
- Dispense IMP to cover the first 4 weeks of the treatment period
- Assist participant in mobile app installation on their smartphone device and provide instructions on completion of eDiary

7.3. Week 2 Visit

This visit will take place 14 days (±3 days) after the Day 1 Visit. Participants may dose at home on the day of the visit. Prior to the visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform brief physical examination
- Measure vital signs
- Collect blood for safety labs as well as inflammatory markers
- Collect urine for urinalysis
- Perform AD rating scales - vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – POEM, and DLQI
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Confirm patient is taking IMP per protocol and is recording this via the eDiary
- Dispense IMP to cover the next 4 weeks of the treatment period

7.4. Week 4 Visit

This visit will take place 28 days (±3 days) after the Day 1 Visit. Participants may dose at home on the day of the visit. Prior to the visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform brief physical examination
- Measure vital signs including weight
- Perform 12-lead ECG
- Collect blood for safety labs
- Collect urine for urinalysis
- Perform urine pregnancy test for WOCPB
- Take digital photographs of the same body locations taken at the Day 1 Visit
- Perform AD rating scales, including vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – HADS, POEM, DLQI, ADCT, and SF-12
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Confirm patient is taking IMP per protocol and is recording this via the eDiary
- Collect empty and unused study wallets/cartons dispensed at the Day 1 Visit
- Dispense IMP to cover the next 4 weeks of the treatment period

7.5. Week 8 Visit

This visit will take place 56 days (±3 days) after the Day 1 Visit. Participants may dose at home on the day of the visit. Prior to the visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform brief physical examination
- Measure vital signs
- Collect blood for safety labs
- Perform urine pregnancy test for WOCBP
- Perform AD rating scales, including vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – POEM, and DLQI
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Confirm patient is taking IMP per protocol and is recording this via the eDiary
- Dispense IMP to cover the last 4 weeks of the treatment period

7.6. Week 12 Visit

This visit will take place 84 days (±3 days) after the Day 1 Visit. Participants may dose at home on the day of the visit. Prior to the visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform brief physical examination
- Measure vital signs
- Collect blood for safety labs
- Perform urine pregnancy test for WOCBP
- Take digital photographs of the same body locations taken at the Day 1 Visit
- Perform AD rating scales, including vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – HADS, POEM, DLQI, ADCT and SF-12
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Confirm patient is taking IMP per protocol and is recording this via the eDiary

7.7. Week 16 Visit

This visit will take place 113 days (±3 days) after the Day 1 Visit. Participants may dose at home on the day of the visit. Prior to the visit, the participant will be asked to withhold the application of the emollient, and where safe, sunscreen and any other topical products until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform full physical examination
- Measure vital signs including weight
- Perform 12-lead ECG
- Collect blood for safety labs as well as serum immune protein markers and inflammatory markers
- Collect urine for urinalysis
- Perform urine pregnancy test for WOCBP
- Take digital photographs of the same body locations taken at the Day 1 Visit
- Perform AD rating scales, including vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – HADS, POEM, DLQI, ADCT and SF-12
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Confirm patient took IMP per protocol and recorded this via the eDiary
- Collect all remaining empty and unused study wallets/cartons dispensed at the Week 2, Week 4 and Week 8 Visits

Open Label Extension Option

Participants who complete the 16 weeks of double-blind treatment may have the option to enter an Open Label Extension (OLE) protocol at the Week 16 Visit, if available. A separate consent form must be signed prior to the Week 16 Visit, however, only those participants that complete all 16 weeks on study IMP (active or placebo) will be allowed to participate in the OLE.

Participants who do not enroll into the OLE will enter a 4-week follow-up period and complete the Week 20 Visit per the SOA.

7.8. Week 20 Follow--Up Visit

This visit will take place 141 days (+3 days) after the Day 1 Visit. Prior to the visit, the participant will be asked to withhold the application of the emollient until after all study assessments have been performed. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed:

- Perform brief physical examination
- Measure vital signs including weight
- Perform 12-lead ECG
- Collect blood for safety labs as well as inflammatory markers
- Collect urine for urinalysis
- Perform urine pregnancy test for WOCBP
- Take digital photographs of the same body locations taken at the Day 1 Visit
- Perform AD rating scales, including vIGA, EASI (and BSA), and SCORAD
- Perform patient reported clinical rating scales – HADS, POEM, DLQI, ADCT, and SF-12
- Review and document concomitant medications and therapies including emollient use
- Assess and document adverse events (AEs)
- Assist the participant to uninstall the mobile application from their smartphone device

7.9. Early Termination Visit

Participants who withdraw prematurely from the study should have an early termination visit using the Early Termination Visit schedule within 14 days of asking to withdraw consent or within 72 hours of starting any AD therapy if their withdrawal was due to treatment failure. The participant will also be asked to have a final telephone call 28 days (+3 days) after taking their last dose of IMP for safety assessments. The date of this telephone call will be considered the end of study date for these participants.

7.10. Unscheduled Visits

Unscheduled visits are visits that fall outside of the scheduled visits indicated in the SOA. These visits and the findings are to be recorded on the appropriate eCRFs.

If an unscheduled visit occurs due to the participant requiring rescue therapy, every attempt should be made to conduct efficacy and safety assessments (e.g., EASI, BSA, vIGA, AEs, and concomitant medications) immediately before prescribing/administering any rescue therapy [**Section 6.9.1.2 Rescue Therapy**].

7.11. COVID-19 Pandemic

Parts or all of this study are expected to run during the COVID-19 pandemic. As a result, a thorough risk analysis has been carried out. In addition, a number of mitigation steps have been considered, for example, the scenarios of individual self-isolation or local/national lockdown.

7.11.1. EDP1815 and Risk of COVID-19 Infection

EDP1815 does not broadly impair either innate or adaptive immune responses, as detailed in a full risk-assessment in Appendix 14.4. Anti-viral responses such as cytotoxic T-cell production of interferon-gamma, innate anti-viral production of interferon-alpha and interferon-beta, and the

generation of high-affinity antibodies are all preserved pre-clinically after treatment with EDP1815. There is no pre-clinical or clinical evidence of EDP1815 causing immunosuppression.

EDP1815 was investigated as a treatment of patients hospitalized with Covid-19 infection (study reference: EDP1815-204 and EDP1815-205), but no safety or efficacy data have yet been reported from these studies.

7.11.2. EDP1815 and COVID-19 Vaccination

As detailed in **Section 6.9.3 Immunizations** of this protocol, live and live-attenuated vaccines should not be given with EDP1815. Non-live and non-replicating vaccines are permitted, and it is not expected that the safety of participants will be impacted by their co-administration. The efficacy of the vaccines co-administered with EDP1815 has not been tested.

7.11.3. EDP1815-207 and COVID-19 Infection

Self-isolation or a positive COVID-19 test in a well subject may not be a reason in itself to stop dosing, as EDP1815 is not expected to increase the risks associated with COVID-19. If a study participant is diagnosed with COVID-19 infection (diagnosed clinically or by laboratory tests), the participant may continue study treatment if the Investigator considers that there is a positive individual risk/benefit balance. This should be discussed with the Medical Monitor.

7.11.3.1. COVID-19 Mitigation Steps

If a participant with COVID-19 must self-isolate or quarantine while on study, and a study visit coincides with this self-isolation or quarantine, the study visit will be missed and the reason the visit was not done recorded in the source documents with COVID-19 isolation / lockdown as the reason for the visit not completed.

In lieu of the study visits, the participant may receive a telephone call to assess adverse reactions, ascertain study IMP status (i.e., did the participant self-interrupt taking IMP) and emollient usage, and collect information on any concomitant medications, including any rescue therapy. Information should be recorded in the participant's source documents and entered into the EDC, as applicable.

The Week 16 study visit should not be missed wherever possible; these visits, therefore, may be conducted outside of the protocol study window. Please contact the Medical Monitor to discuss further.

7.12. Missed Visits and Procedures

Missed visits and any procedures not performed (not attempted) for reasons other than screen failure, illness, injury or progressive disability (i.e., subject is physically unable to perform test) will be reported as protocol deviations.

A major protocol deviation will be recorded for missed visits and any procedures not performed (not attempted) for Day 1 and Week 16 visits, regardless the reason the visit was missed.

Procedures or visits not performed due to screen failure, illness, injury or disability, including procedures that were attempted but failed (i.e., blood samples unable to be drawn after multiple attempts) will not be reported as protocol deviations.

8. EFFICACY ASSESSMENTS

Assessments will be performed at designated time-points throughout the study for efficacy evaluations. In addition to the assessments below, participants will provide information on their demographics and smoking history, past medical history (including diagnosis of atopic dermatitis), as well as concomitant medication usage.

All efficacy assessments will be completed at the study site utilizing a site tablet at the specified visits as indicated on the SOA. The site staff will assist the participant in completing those assessments that are considered patient reported outcomes (PRO). The same reviewer should conduct the skin assessments wherever possible for a single participant, and if not possible, at a minimum, the same reviewer performs the Day 1 and Week 16 assessments for that participant.

The Investigators and site staff will be provided with further details on how to perform the following assessments and how to calculate each of the scores (if applicable).

8.1. Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) is a validated measure of eczema severity, which considers a combination of the body surface area affected across 4 body regions, and the severity of the clinical signs of erythema, oedema/induration, excoriation and lichenification (Eczema, n.d.). The EASI score ranges from 0 – 72 (EASI, 2017 Jan). EASI-50, EASI-75, EASI-90 responses are defined as at least 50%, 75% and 90% decrease from baseline EASI score respectively.

EASI is the core outcome for measuring the clinical signs of AD in all AD trials, as selected by the Harmonising Outcome Measures for Eczema (HOME) group. The EASI score will be assessed to determine the treatment effect of EDP1815 compared to placebo.

8.2. Validated Investigator's Global Assessment

The Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA) will be used to describe the overall appearance of lesions at a given time-point (Simpson E, 2020 Sep). There is a standardised grading system based on an overall assessment of the degree of erythema, papulation/induration, lichenification, and oozing/crusting. In indeterminate cases, extent will be used to differentiate between scores – but otherwise extent is not used in the scoring system. The vIGA score ranges from 0 (Clear skin) to 4 (Severe disease).

8.3. SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (SCORAD) is a clinical tool which is also used to assess the extent and severity of eczema, to assess treatment effects. There is an investigator-rated area score which uses the rule of nines to assess disease extent, and a disease intensity score comprising erythema, swelling, oozing/crusting, excoriation, lichenification, and dryness. Additionally, there is a subjective symptoms component which considers itch and sleeplessness scored using a visual analogue scale. These scores combine to give a SCORAD score between 0 – 103 (Dermatitis, 1993).

8.4. Patient Oriented Eczema Measure

The Patient Oriented Eczema Measure (POEM) is a simple PRO assessment tool for monitoring disease severity. It includes a series of 7 questions, measuring itch, sleep, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness over the last week, and is scored by the participant. Each of the 7 questions is scored from 0 (no days) to 4 (every day), giving a POEM score range from 0 to 28, with higher scores representing higher disease severity (Charman, 2004 and Charman, 2013). The minimally clinically important difference threshold is a change of ≥3.4 points on average (Schram, et al., 2011). For the purposes of changes within an individual participant, a response will therefore be considered to be a ≥4-point change from baseline.

8.5. Dermatology Life Quality Index

This is a validated patient reported outcomes instrument comprised of 10 questions to assess how a participant's skin disease has affected their quality of life over the past week (Finlay AY, 1994). The DLQI score ranges from 0 to 30, with higher scores indicating greater impairment of quality of life. A DLQI score of 0 or 1 is considered as having no effect on a patient's quality of life, and a 4-point change from baseline is considered the minimal clinically important difference threshold (Basra, 2015).

8.6. Peak Pruritus Numerical Rating Scale (PP-NRS)

The Peak Pruritus Numerical Rating Scale (PP-NRS) is a scale from 0 ("no itch") to 10 ("worse imaginable itch") for participants to rate their worst itch that they have experienced over the previous 24 hours (Phan, 2011). The PP-NRS will be completed daily question via a daily questionnaire from the Screening Visit to the Week 16 visit. A ≥2-4-point change from baseline is considered the minimally clinically important difference threshold (Yosipovitch, et al., 2019).

8.7. Sleep Disturbance Numerical Rating Scale (SD-NRS)

The Sleep Disturbance Numerical Rating Scale (SD-NRS) is a scale from 0 ("best possible sleep") to 10 ("worse possible sleep") for participants to rate their worst sleep that they have experienced over the previous 24 hours. The SD-NRS will be completed via a daily questionnaire from the Screening Visit to the Week 16 visit. A ≥2 point change from baseline is considered the minimally clinically important difference threshold (Dias-Barbosa, Matos, & Vernon, 2020).

8.8. Body Surface Area

The Body Surface Area (BSA) is a measure of the extent of atopic dermatitis at a given time. It is calculated by estimating the number of participant's handprints of active atopic dermatitis are present where one handprint (including digits) represents 1% body surface area. The BSA provides another assessment of disease severity by looking at coverage of body surface and is sometimes assessed as a product of the vIGA*BSA as a further marker of disease severity and response to treatment (Suh, 2020).

8.9. 12-Item Short Form Health Survey

The 12-Item Short Form Health Survey (SF-12) is a PRO instrument consisting of twelve questions used to measure non-disease related outcomes in 8 health domains, including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social functioning, and mental health. The score (ranging from 0 to 100) is presented in two components: a mental composite scale (MCS) and physical composite scale (PCS). The

higher the score, the better the physical and mental health functioning. The SF-12 scores have been shown to correlate with those of the 36-Item Short Form Health Survey (SF-36) (Ware J, 1996).

8.10. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a PRO instrument used to measure anxiety and depression over the past week. It is comprised of 7 questions for anxiety and 7 questions for depression and each are scored using a 4-point Likert scale (e.g., 0-3). Scores for each domain therefore range from 0-21, where 8-10 is mild, 11-14 is moderate and 15-21 is severe anxiety or depression (Snaith, 2003).

8.11. Atopic Dermatitis Control Tool

The Atopic Dermatitis Control Tool (ADCT) is a 6-question PRO instrument used to detect change of disease activity in a person over time. There are six main areas that assess the multi-dimensional aspects of disease control over the course of a week, scored between 0-4, with a minimum score of 0 and a maximum score of 24. A higher score indicates lower AD control. A change of 5 points is the threshold for meaningful within person change, where a decrease of 5 or more points indicates clinically relevant improvement of AD control and an increase of 5 or more points indicates a clinically relevant worsening of AD control (Pariser, 2020).

9. SAFETY ASSESSMENTS

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable regulations and International Conference on Harmonization (ICH) guidelines. The Investigator will carefully monitor each subject throughout the study for possible adverse events.

9.1. Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the participant's history or from Day 1.

9.1.1. Adverse Events of Special Interest

There are no prespecified AEs of special interest (AESI) for this study.

9.2. Adverse Drug Reactions

Adverse drug reactions (ADR) (also known as suspected unexpected adverse drug reactions or SUSARs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs or SUSARs, if there is a causal relationship to the medicinal product.

9.3. Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

- Results in death.

- Is life threatening; that is, poses an immediate risk of death as the event occurred.
  - This serious criterion applies even if the participant, in the view of the Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - A participant admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious (e.g., life threatening adverse experience, important medical event).

  - Hospitalizations for reasons not associated with the occurrence of an AE (e.g., preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting.
    - For example, if a participant has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria.
    - Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

- Results in persistent or significant disability or incapacity.
  - This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the participant's ability to carry out normal life functions.

- Results in a congenital anomaly or birth defect in the offspring of the participant (whether the participant is male or female).

- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.4. Reporting and Recording AEs

The Investigator will carefully monitor each participant throughout the study for possible AEs. In order to ensure complete safety data collection, all AEs occurring during the study (i.e., after the signing of the Informed Consent form), including the pre-treatment period required by the protocol, must be reported in the CRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All AEs will be collected and reported in the electronic data capture (EDC) system and compiled into reports for periodic reviewing by the Medical Monitor. The Medical Monitor shall promptly review all information relevant to the safety of the investigational product, including all serious adverse events (SAEs). Special attention will be paid to those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor (or designee).

Serious AEs that occur more than 30 days after the last dose of IMP need not be reported unless the investigator considers them related to the IMP.

9.4.1. Assessment of AEs

Adverse events will be solicited in a consistent manner at every study visit. Participants will be asked uniform open-ended questions to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (prescription or OTC medications), noticed any changes in bowel habits or had unplanned visits to their general practitioner since the last visit.

In addition to participant observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents (e.g., participant diaries) that are relevant to participant safety will be documented on the AE page in the CRF.

If the participants reports an adverse event, the following will be recorded in the source and on the eCRF:

1. Description of the event
2. Date and time of onset and resolution (duration)
3. Record grading as per appropriate toxicity scale
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product
6. Action taken regarding investigational product
7. Outcome
8. If any Concomitant Medications were given
9. Whether the AE resulted in participant withdrawal from the study
10. Investigator-specified assessment if the AE is related to a recent/current COVID infection
11. If a COVID positive PCR test received within the last 14 days

Signs or symptoms of a participant's atopic dermatitis should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the participant's history.

9.4.2. Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities or their health. The intensity of the AE will be rated in accordance with the CTCAE Version 5.0. Adverse events related to temperature and abnormal laboratory results that are not found in the CTCAE Version 5.0 will be rated in accordance with the FDA Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* [**Appendix 14.5 Toxicity Grading Scale**].

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

9.4.3. Assessment of Causality

The investigator's assessment of an AE's relationship to IMP is part of the documentation process. Regardless of the investigator's assessment of an AE's relationship to IMP, the AE must be reported.

The relationship or association of the IMP in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: There is no association between the IMP and the reported events.

Possible: Treatment with the IMP may have caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the IMP but could also have been produced by another factor.

Probable: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the IMP seems likely. The event disappears or decreases on cessation or reduction of the dose of IMP.

Definite: A definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the IMP is re-administered.

9.4.4. Description of Adverse Events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the participant's own words on his/her own records (e.g., diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF are described in the eCRF Completion Guidelines.

9.4.4.1. Rule for Repetition of an AE

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening".
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one.

9.5. Reporting Serious Adverse Events

Serious Adverse Events (SAEs) must be reported to the Medical Monitor and Sponsor immediately, without undue delay but no later than within 24 hours of the site learning of the SAE.

To report the SAE, the investigator must record the SAE on the AE eCRF in the EDC system as well as any relevant CRF forms (e.g., drug dispensation CRF, applicable laboratory CRF). When the AE CRF is completed, [redacted] personnel will be notified electronically automatically and will retrieve the form.

If the event meets serious criteria and it is not possible to access the EDC system, please complete the back-up paper SAE Form in English with as much information that is known at the time and send it by e-mail to [redacted], or call the [redacted] SAE hotline and fax the completed paper SAE Form to [redacted] immediately, without undue delay but no later than within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

The Sponsor has the legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

An Investigator who receives a safety notification letter describing a SUSAR or other specific safety information from the Sponsor, will review and will notify the local IRB/IEC, if appropriate according to local requirements.

9.5.5. Follow Up of Adverse Events

All AEs must be followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, the event is considered stable, the participant dies, or the participant is lost to follow-up. However, any new AEs that start more than 28 days after the final dose and changes in AEs that occur after the participant's end of study visit will not be recorded in the eCRF.

9.6. Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that a IMP may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation or up to 28 days after the final dose of IMP must be reported to [redacted] by phone or email, within 2 weeks of learning of its occurrence. [redacted] will send the Exposure in Utero Form to the site for completion within 24 hours. This form should be completed and returned to [redacted] within 24 hours of receipt.

All SAEs occurring in association with a pregnancy, brought to the Investigator's attention after the participant has completed the study must be promptly reported to [redacted]

Please see Appendix 14.3 Contraceptive Guidance and Collection of Pregnancy Information for further information.

9.7. Overdose

Excessive dosing (greater than 4 capsules within 24 hours) should be recorded in the CRF. Participants will be instructed to contact the Investigator or study coordinator immediately in the event of a suspected overdose.

Any overdose must be promptly reported to [redacted] via the Special Situations Form. Overdose itself is not to be reported as an AE. However, any AEs or SAEs associated with the overdose are to be reported on relevant AE/SAE sections in the eCRF and on the Paper SAE Form provided to [redacted] (**Section 9.5 Reporting Serious Adverse Events**).

In the event of a symptomatic overdose, the Investigator should:

1. Manage the patient symptomatically with supportive care.
2. Contact the Medical Monitor urgently.
3. Document the quantity of the excess dose in the eCRF.
4. Document the overdose symptoms and their duration in the eCRF.

Doses of EDP1815 capsules that have previously been administered include a dose of 8.0 x 10^{11} cells taken once daily for 16 weeks, and 1.28 x 10^{12} cells taken once daily for 8 weeks. There are no specific expected adverse events expected in an overdose, but the participant should be closely and carefully monitored. There is no specific treatment or antidote, but supportive clinical care should be provided as dictated by the participant's clinical status.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.8. Safety Signal Detection

Selected data from this study will be reviewed periodically in a blinded fashion to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs. [redacted]DM will perform ongoing SAE reconciliations in collaboration with the PV representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at the Sponsor may identify additional safety measures (e.g., AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

9.9. Study Halting Criteria

The study will be halted if any of the following occur:

- One fatal SAE considered definitely, probably, or possibly related to the investigational product.

- Two or more participants with a non-fatal SAE considered definitely, probably, or possibly related to the investigational product.

- Three or more participants with grade 3 AEs of the same type considered definitely, probably, or possibly related to the investigational product.

- Any participant develops a documented *Prevotella histicola* infection in a sterile space confirmed by clinical culture and/or qPCR.

9.10. Laboratory Measurements

Standard laboratory analyses to understand safety and tolerability include the following measurements:

Hematology	Biochemistry	Urinalysis
Complete Blood Count with differentials:	Alanine Aminotransferase (ALT)	Bilirubin
Hemoglobin	Aspartate Aminotransferase (AST)	Blood
Hematocrit	Creatinine	Glucose
Platelet count	C-Reactive Protein (CRP)	Ketones
Red blood count (with percent reticulocytes)	Gamma-glutamyl transpeptidase (GGT)	Nitrites
Mean Corpuscular Hemoglobin (MCH)	Potassium	pH
Mean Corpuscular Hemoglobin Concentration (MCHC)	Sodium	Protein
Mean Corpuscular Volume (MCV)	Total Bilirubin	Specific Gravity
White blood cell count:	Urea	
Basophils		
Eosinophils		
Lymphocytes		
Monocytes		
Neutrophils		

A serum pregnancy test will be performed on women of childbearing potential (WOCBP) at the Screening Visit. Urine pregnancy testing will be conducted on Day 1 and then monthly thereafter.

Additional testing may be ordered if needed, to further assess an adverse event (AE), or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

Only abnormal laboratory test results (hematology, clinical biochemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital sign measurements), which are clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs.

A central laboratory (or specialized central laboratories) will be used for all laboratory analyses. Details of sample collection and handling procedures will be provided in the specific laboratory manual.

9.10.1. Review of Laboratory Measurements

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of IMP should be repeated until the values return to normal or baseline value or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in this section, must be conducted in accordance with the laboratory manual and the SOA. Screening laboratory results will be used to confirm eligibility at Day 1. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded on the Adverse Events eCRF.

9.10.2. Blood Volumes

The planned maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 145 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The planned maximum amount of blood collected from each participant at a single visit will not exceed 25 mL, and the planned maximum amount of blood collected from each participant over 30 days will not exceed 48 mL.

9.11. Biomarkers

9.11.1. Genetic Testing

Optional blood samples may be collected at Day 1 for genetic testing, such as human leukocyte antigen (HLA) typing and whole genome sequencing (WGS). The data will be used to correlate with the clinical outcomes in order to identify patient group(s) who may benefit the most from EDP1815 treatment. Only genetic variants that cause different responses to EDP1815 will be assessed. This sample will be stored for a maximum of 10 years and will be destroyed if not used within this time. This is an optional collection sample where local regulations and IRBs/IECs allow. This sample will only be collected on those participants who consent to participate in this optional blood collection for genetic testing.

9.11.2. Immune Protein Markers

Immunoglobulin E (IgE) are antibodies produced by the immune system and are often raised in patients with AD, particularly with the phenotype known as 'extrinsic' AD (Renert-Yuval, 2021). IgE is a recognized biomarker of disease severity in AD and is regularly measured in clinical practice. It is being measured in participants to see if treatment response can be predicted by Day 1 IgE level, and also whether IgE levels improve on treatment as a biomarker of treatment success. In addition to the IgE levels, other immune protein markers such as cytokines may be measured from this sample in order to assess the anti-flammatory and disease-modifying effects of EDP1815. These samples will be collected at Day 1 and Week 16.

9.11.3. Transcription Analysis

RNA will be collected from whole blood samples at Day 1, Week 2, Week 16 and Week 20 to quantify inflammation markers in immune cells to assess the effect of EDP1815. These samples may be analyzed subject to the clinical data in the trial. The genes to be analyzed may include those related to host immune response as well as those related to the disease pathology.

9.11.4. Microbiome Sample

A fecal sample will be collected within 7 days of Day 1 to enable microbiome sampling. The purpose of this sample will be to perform analysis of stool bacterial DNA, to see if there is a correlation between background microbial content in the large intestine, and response to treatment with EDP1815. Participants will be provided with a fecal collection kit and instructions at the Screening Visit with instructions to bring the sample in at their Day 1 visit. Any participant that enrolls in the study under Protocol Version 5.0 is not required to provide a fecal sample.

9.12. Other Safety Measurements

9.12.1. Vital Signs, Height and Weight

Vital signs will be obtained after the participant has been in a seated position for approximately 5 minutes. Vital signs, including systolic and diastolic blood pressure, pulse rate (radial artery)/minute, respiratory rate/minute, and temperature. Height will be measured and recorded at the Screening Visit only. Weight will be assessed at specified visits (without shoes and street clothing). Body mass index will be calculated from the height and weight. Investigators should pay special attention to clinical signs related to previous serious illness.

9.12.2. Physical Examination

A physical examination (PE) will be performed and recorded in source at specified visits. Only abnormal, clinically significant findings will be recorded as AEs on the eCRF.

The following systems will be examined when a full PE is indicated: general appearance, cardiovascular, respiratory, gastrointestinal, musculoskeletal, central nervous system, lymph nodes and skin.

The following systems will be examined when a brief PE is indicated: general appearance, cardiovascular, respiratory, gastrointestinal and skin.

9.12.3. 12-Lead Electrocardiogram

A single 12-lead electrocardiogram (ECG) will be obtained at specified visits using an ECG machine that automatically calculates heart rate and measures PR, RR, QRS, and QT interval. QTcF (Fridericia) intervals will be auto derived and populated in the case report form (CRF).

A single ECG tracing is to be obtained on the day of the visit after the participant has been in a lying position for approximately 5 minutes. If in the opinion of the Investigator, there appear to be clinically significant findings, it should be repeated. If the repeated tracing also appears clinically significant, the Investigator should report the abnormality as an AE and consult with the Medical Monitor to decide whether the participant should continue treatment in the study.

9.13. Non-Safety Measurements

9.13.1. Digital Photography

Digital photographs should be taken of the upper and lower body (upper & lower anterior and upper & lower posterior) as half body shots at Day 1. Additional photographs of up to six specific body areas, i.e., limbs, trunks, and back, will also be taken. The same locations photographed at Day 1 should be followed through the study for each participant.

Procedural details for digital photography will be provided to the sites.

10.STUDY MANAGEMENT AND ADMINISTRATION

10.1. Adherence to protocol

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator. A significant deviation occurs when there is non-adherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

The Investigator should not deviate from the protocol. However, the Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, where required. The deviation should be well documented in the participant's source documentation.

In order to keep deviations from the protocol to a minimum, the Investigator and relevant site personnel will be trained in all aspects of study conduct by the Sponsor or Sponsor representative. This training will occur either as part of the Investigator's Meeting or Site Initiation Visit (SIV). Ongoing training may also be performed throughout the study during routine site monitoring activities.

10.2. Monitoring

Monitoring of the study will be delegated by the Sponsor to [redacted] the Clinical Research Organization (CRO) handling project, data and site management. [redacted] will monitor the study to meet their monitoring Standard Operating Procedures (SOPs), the monitoring plan, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

The Investigator and site staff are expected to cooperate with the Sponsor and [redacted] and to be available during the monitoring visits (whether onsite or remote, if needed) to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct, secure access to source data/documents for study -related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow the Sponsor or [redacted] to periodically review all eCRFs and corresponding source documents (e.g., hospital and laboratory records for each study participant). Monitoring visits (whether onsite or remote, if needed) will provide the Sponsor and [redacted] with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol requirements, applicable authorities regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

10.2.1. Definition of Source Data

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts,

pharmacy records, care records, ECG or other printouts, completed scales, quality of life questionnaires, certified copies or video, for example. Source documents should be kept in a secure, limited access area.

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of CRFs are not considered acceptable source documents.

The following data will be considered as electronic source and therefore, will not be recorded directly into the EDC and will not appear in a separate source document as defined above. However, paper source documents may be utilized for collection of PROs and COAs listed below should there be an unforeseeable circumstance (such as a power outage) and the electronic source is unavailable. Any information about a participant that is collected during this study will remain secured and confidential and will be handled per applicable regulations (i.e., data collected via mobile applications).

- Participant Electronic Diary (eDiary) including IMP, emollient and rescue therapy usage and PP-NRS and SD-NRS daily questionnaire. A paper diary will be utilized between the Screening and Day 1 Visits to collect participant information on emollient usage, participant's worst itch and participant's sleep.

- Patient Reported Outcome Measurements (PROs), including POEM, DLQI, ADCT, SF-12, and HADS.

- Clinician Outcome Assessments (COAs) including EASI, BSA, vIGA, and SCORAD.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (e.g., ECG reports, laboratory reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

10.2.2. Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., participant files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in **Section 10.2.1 Definition of Source Documents**.

10.3. Data Management

10.3.1. Data Quality Assurance

This study will be conducted according to ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this

study will be documented and will comply with the current ICH guidance on quality and risk management. The Sponsor assumes accountability for actions delegated to [redacted]

10.3.2. Case Report Form Completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic CRFs and in all required reports. Any change or correction to the CRF after saving must be accompanied by a reason for the change. Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator. The Investigator should maintain a list of personnel authorized to enter data into the electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.3.3. Data Entry and Reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database that is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual username and password that allows for record traceability.

Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. A quality review of the data will be performed by the site with additional reviews by the clinical monitor through source data verification.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

Paper copies of the eCRFs and other database reports may be printed by the investigator. This system provides site staff, monitors, and reviewers with access to hard copy audits, discrepancy reviews, and investigator comment information.

After all data reviews and query resolutions are complete, the SAP is approved and signed, and any summary/analysis populations are approved, the database will be locked.

10.3.4. Participant Screening & Enrollment Log/Participant Identification Code List

The participant's Screening and Enrollment will be recorded in the Participant Screening and Enrollment Log.

The Investigator will keep a Participant Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each participant.

The participant's consent and enrollment in the study must be recorded in the participant's medical record. These data should identify the study and document the dates of the participant's participation.

10.4. Termination of the Study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for any reason including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, the Sponsor (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP/investigational device and other material in accordance with the Sponsor's procedures for the study.

10.5. Archiving and Data Retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP/investigational device. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with the Sponsor (EMEA, 2002 Jul).

The Investigator will contact the Sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify the Sponsor in writing should he/she relocate or move the study--related files to a location other than that specified in the Sponsor's Trial Master File (TMF).

10.6. Audit and Inspection

The Investigator will permit study--related audits mandated by the Sponsor, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the participants enrolled have been protected, that enrolled participants (i.e., signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP/investigational device have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform the Sponsor (or designee).

10.7. Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

11.STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan.

11.1. Definition of Analysis Sets

The following analysis sets will be used in the statistical analyses.

11.1.1. Participant Analysis Sets

Enrolled set: The enrolled set will consist of all participants who sign the ICF.

Full analysis set: The FAS set will consist of all participants who were randomized to treatment. All analyses using the FAS will group participants according to randomized treatment.

Safety analysis set: The SAS will consist of all participants who received any IMP. All analyses using the safety set will group participants according to treatment received.

11.1.2. Defined Data Point Sets

The following efficacy data point sets (EDPS) and safety data point sets (SDPS) are defined:

EDPS1: Consists of all data collected at a scheduled timepoint that is at least 28 days after use of topical corticosteroid rescue therapy. Data collected less than 28 days after such use or data missing due to withdrawal from the study for reasons considered related to study medication will be replaced as follows:

- Continuous endpoints: value will be imputed with the last off-rescue observation carried forward (off-rescue is defined as data collected at least 28 days after use of rescue medication)
- Responder endpoints: value will be imputed as non-response.
- Count endpoints: N/A (No count endpoint will use this DPS).

Data missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

EDPS2: Consists of all data collected at a scheduled timepoint that is at least 28 days after use of topical corticosteroid rescue therapy. Data collected less than 28 days after such use will be considered as missing and excluded from the analysis. Data missing due to withdrawal from the study for reasons considered related to study medication will be imputed as per DPS1. Data missing for other reasons will not be replaced.

EDPS3: Consists of EASI-50 responses collected at Week 16 that were evaluated at least 14 days after use of topical corticosteroid rescue therapy. Data collected less than 14 days after such use or missing due to withdrawal from the study for reasons considered related to study medication will be imputed as non-response.

EASI-50 response missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

EDPS4: Consists of EASI-50 responses collected at Week 16 that were evaluated at least 28 days after use of topical corticosteroid rescue therapy. Data collected less than 28 days after such use will be replaced as per DPS1. Data missing due to other reasons including early withdrawal from the study for any reason will not be replaced and be considered as missing.

EDPS5: Is a subset of DPS1 for the EASI-50 response data only, excluding any data collected or imputed after the use of a prohibited medication or the unblinding of a participant (whichever occurs first) and excluding all data from subjects who take <75% of expected doses or whose compliance with emollient use was <75% or did not complete the 12-week treatment period.

EDPS6: Consists of data collected in the absence of topical corticosteroid rescue therapy at any time since Day 1 for the responder endpoints relating to EASI, vIGA and PP-NRS. Data collected after such use or missing due to withdrawal from the study for reasons considered related to study medication will be imputed as non-response.

Responses missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

EDPS7: Contains all data collected as part of a count endpoint. A treatment policy strategy will be used for all intercurrent events other than discontinuation from the study which will use a while on treatment strategy (i.e., the collection period will be ended at the time of study discontinuation).

SDPS1: Consists of all observed data collected at a scheduled visit.

SDPS2: Consists of all observed data collected, including data from scheduled and unscheduled visits.

The FAS with EDPS1 are used to estimate the primary estimand and all secondary and exploratory estimands (excluding those relating to count endpoints).

The FAS with EDPS2-EDPS6 will be used to estimate supplementary estimands for the primary endpoint. The FAS with EDPS2 and EDPS6 will be used to estimate supplementary estimands for selected secondary estimands.

The FAS with EDPS7 are used to estimate the secondary estimands relating to count endpoints.

The SAS and SDPS1 are used to present safety data assigned to specific scheduled visits.

The SAS and SDPS2 are used to present all other safety data, including adverse events.

Note that all subjects who withdraw from the study prematurely will be evaluated prior to database lock and unblinding will have their reason for withdrawal evaluated as being related or non-related to study medication.

11.2. General Statistical Considerations

Statistical analysis will be performed using SAS software Version 9.3 or later.

Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Daily time to event response endpoints will be summarized using the Kaplan-Meier estimates of the proportion of responders in each study week together with the estimated median and quartiles for time to response.

Descriptive statistics will also be used extensively in figures to visualize the data. These include but are not limited to mean (SE) or LS Mean (95% CI) plots against time, waterfall plots for individual changes at a specific time point, vertical bar plots showing percentages of responders and Kaplan-Meier plots.
Data will be listed in data listings.

Baseline will be defined as the last non-missing data available prior to the first dose of IMP. Data on Day 1 will be assumed to have been collected before first dose of IMP.

The subgroup of participants with IGA=3 at Day 1 will be used to perform subgroup analyses on the primary estimand. Data for the subgroups defined by IGA=2 and IGA=4 at baseline will be summarized but no analysis done as the sample sizes are not expected to be large enough for meaningful comparisons to be made.

The focus of this study is on model estimation of treatment effects and as such no adjustments will be made for multiple testing in this study.

Two sets of tables, figures and listings will be provided, one for the combined analysis of Cohorts 1-3 and one for the analysis of Cohort 4.

<u>Cohort 1-3 Analysis</u>
The placebo participants from Cohorts 1, 2 and 3 will be pooled and compared to the following active treatment groups:

- EDP1815 $1.6x10^{11}$ QD (Cohort 1)
- EDP1815 $6.4x10^{11}$ QD (Cohort 2)
- EDP1815 $3.2x10^{11}$ BID (Cohort 3)
- EDP1815 $6.4x10^{11}$ Daily (Cohorts 2 and 3)
- All EDP1815 (Cohorts 1, 2 and 3)

For the primary analysis, the first three comparisons using the individual cohorts only will be considered as primary with the pooled active comparisons considered as secondary.

The following comparisons between active treatment groups will also be performed but will be considered as exploratory in nature:

- EDP1815 $6.4x10^{11}$ QD (Cohort 2) vs EDP1815 $3.2x10^{11}$ BID (Cohort 3)
- EDP1815 $1.6x10^{11}$ QD (Cohort 1) vs EDP1815 $6.4x10^{11}$ QD (Cohort 2)

<u>Cohort 4 Analysis:</u>

The analyses for Cohort 4 will compare EDP1815 $8.0x10^{10}$ to a combined control group including the Cohort 4 placebo participants (approximately 35) and set of matched placebo participants from Cohorts 1-3 (approximately 35). This will provide a total of approximately 70 placebo participants, resulting in a 1:1 comparison between EDP1815 $8.0x10^{10}$ and placebo. This combined placebo cohort will be referred to as the Cohort 4 Matched Placebo group.

While not enrolled concurrently to Cohort 4, the Cohort 1-3 placebo group provides an appropriate population to supplement the Cohort 4 placebo group, increasing the power of the comparison of EDP1815 $8.0x10^{10}$ to placebo and precision of the treatment effect estimates (Viele, 2014). A propensity-score based matching algorithm will be used to select patients from the Cohort 1-3 Placebo group in to order balance key baseline characteristics (Austin, 2011). Matching will be performed based on propensity scores derived from baseline characteristics such as IGA, EASI score, BSA, gender, and country. Full details of the matching algorithm are provided in the SAP.

Summary tables for Cohort 4 will include a column for the Cohort 4 Only Placebo group in addition to columns for the Cohort 4 Matched Placebo group as well as the EDP1815 $8.0x10^{10}$ group.

Analysis tables and figures will include only the Cohort 4 Matched Placebo group and the EDP1815 $8.0x10^{10}$ group and all primary and secondary comparisons will be between these two groups.

As an exploratory analysis, analyses may be repeated including the EDP1815 $1.6x10^{11}$ QD (Cohort 1) treatment group in the statistical models for Cohort 4. For these analyses the comparison of interest will be between the two active EDP1815 treatment groups (Cohort 1 vs Cohort 4).

11.3. Estimands and Intercurrent Events

11.3.1. Primary Estimand and Supplementary Estimands of the Primary Objective

The primary estimand and the supplementary estimands for the primary objective will consider the effect of each individual EDP1815 cohort compared to the relevant placebo group (Cohort 1-3 Pooled Placebo for comparisons to C1-3 EDP1815 groups; and Cohort 4 Matched Placebo for comparison to the Cohort 4 EDP1815 group) on the percentage of participants achieving EASI-50 at Week 16.

The population summary measure of interest will be the odds ratio between each active EDP1815 treatment group and the relevant placebo group.

The FAS participant analysis set will be used.

Strategies for intercurrent events will be accounted for in the following manner using the relevant EDPS as follows:

Table 11-1: Intercurrent Event Strategies for the Primary and Supplementary Estimands

Estimand	Efficacy Data Point Set	Intercurrent Events		
		Use of Permitted Topical Corticosteroid Rescue Therapy	Study Discontinuation Before Week 16 Visit	Use of prohibited medications, non-compliance or unblinding Before Week 16
Primary Estimand	EDPS1	If <28 days before Week 16 visit: Composite Strategy Participant will be considered a non-responder If ≥28 days before Week 16 visit: Treatment Policy Strategy Data will be used as collected	If due to related reason: Composite Strategy Participant will be considered a non-responder If due to non-related reason: While-on-treatment strategy No replacement of missing data	Treatment policy strategy: Data will be used as collected
Supplementary Estimand 1	EDPS2	If <28 days before: While-on-treatment Strategy Data will be considered missing If ≥28 days before: Treatment Policy Strategy Data will be used as collected	As per primary estimand	As per primary estimand
Supplementary Estimand 2	EDPS3	If <14 days before Week 16 visit: Composite Strategy Participant will be considered a non-responder If ≥14 days before Week 16 visit: Treatment Policy Strategy Data will be used as collected	As per primary estimand	As per primary estimand
Supplementary Estimand 3	EDPS4	As per primary estimand	While-on-treatment strategy: No replacement of missing data	As per primary estimand
Supplementary Estimand 4	EDPS5	As per primary estimand unless data is already excluded due to use of prohibited medications, non-compliance or unblinding	As per primary estimand unless data is already excluded due to use of prohibited medications, non-compliance or unblinding	While-on-treatment strategy Data collected after the intercurrent event will be excluded

Estimand	Efficacy Data Point Set		Intercurrent Events	
		Use of Permitted Topical Corticosteroid Rescue Therapy	Study Discontinuation Before Week 16 Visit	Use of prohibited medications, non-compliance or unblinding Before Week 16
Supplementary Estimand 5	EDPS6	Composite strategy Participants with use at any time between Day 1 and the Week 16 visit will be considered as non-responders.	As per primary estimand	As per primary estimand

11.3.2. Secondary Estimands

All continuous and response secondary estimands will use EDPS1 which uses a composite strategy for the use of topical corticosteroid rescue therapy less than 28 days before the relevant visit and for data missing due to withdrawal from the study due to a reason considered as related to study medication. For intercurrent events relating to compliance with the study medication, emollient use, unblinding or use of prohibited medications, a treatment policy strategy and data will be analyzed as collected.

Secondary endpoints based on the EASI, vIGA and PP-NRS endpoints will be analyzed with a supportive estimand using EDPS2, which uses a while-on-treatment strategy for rescue medication and excludes any data collected less than 28 days after rescue medication use. In addition, for responder endpoints relating to EASI, vIGA and PP-NRS a further supportive estimand using EDPS6 will be analyzed where all timepoints after any use of rescue medication will be considered as a non-responder.

Secondary count endpoints will use EDPS7 which includes all data as collected prior to completion or withdrawal from the study. As rescue medication use forms part of these endpoints it is not considered as an intercurrent event.

The following treatment differences will be estimated for each estimand in Cohorts 1-3:

- EDP1815 $1.6x10^{11}$ QD (Cohort 1) vs Cohorts 1-3 Pooled placebo
- EDP1815 $6.4x10^{11}$ QD (Cohort 2) vs Cohorts 1-3 Pooled placebo
- EDP1815 $3.2x10^{11}$ BID (Cohort 3) vs Cohorts 1-3 Pooled placebo
- EDP1815 $6.4x10^{11}$ Daily (Cohorts 2 and 3) vs Cohorts 1-3 Pooled placebo
- All EDP1815 (Cohorts 1, 2 and 3) vs Pooled placebo
- EDP1815 $6.4x10^{11}$ QD (Cohort 2) vs EDP1815 $3.2x10^{11}$ BID (Cohort 3)*
- EDP1815 $1.6x10^{11}$ QD (Cohort 1) vs EDP1815 $6.4x10^{11}$ QD (Cohort 2)*

* The final two comparisons between active treatment groups will be considered as exploratory and only estimates and confidence intervals of such comparisons will be shown.

The following treatment differences will be estimated for each estimand in Cohort 4:

- EDP1815 $8.0x10^{10}$ QD (Cohort 4) vs Cohort 4 Matched Placebo
- EDP1815 $8.0x10^{10}$ QD (Cohort 4) vs EDP1815 $1.6x10^{11}$ QD (Cohort 1)**

** The comparison between Cohort 4 and Cohort 1 active treatments will be performed on the primary and selected secondary endpoints in a separate model that also includes the EDP1815 $1.6x10^{11}$ QD (Cohort 1) treatment group, these comparisons will be considered as exploratory and only estimates and confidence intervals of such comparisons will be shown.

All secondary estimands will be evaluated at Weeks 4, 8, 12 and 16 unless otherwise specified.

Summary statistics only will be shown at Week 20 for those participants who completed treatment but did not wish to participate in the OLE.

Secondary efficacy estimands will be constructed for the following endpoints:

Table 11-2: Secondary Estimand Details

Data Type	Endpoint	Population Summary Measure of Interest
Continuous	Change and percentage change from baseline in EASI score[1], Change and percentage change from baseline in IGA*BSA[1] Change and percentage change from baseline in BSA Change and percentage change from baseline in SCORAD score Change and percentage change from baseline in DLQI score Change and percentage change from baseline in POEM score, Change from baseline in PP-NRS[1,3] score Change from baseline in SD-NRS[2]	Mean difference between treatments
Response	EASI-50[1,2], EASI-75[1,2], EASI-90[1,2] IGA of 0 or 1 with a ≥2 point improvement from baseline[1,2] IGA of 0 or 1[1,2] IGA of 0 (at Week 12 and 16 only)[1,2] BSA-50, BSA-75 BSA ≤3% SCORAD-50, SCORAD-75 Improvement of ≥4 points in DLQI from baseline[4] Improvement of ≥2 and ≥4 points in PP-NRS score from baseline[1,2,3,4] Improvement of ≥2 points in SD-NRS score from baseline[3,4] Improvement of ≥4 points in POEM score from baseline[4] No requirement for rescue therapy[5]	Odds ratio between treatments
Count	Number of courses of rescue therapy[6] Number of days requiring rescue therapy[5]	Rate ratio between treatments

[1] These endpoints will also have secondary supplementary estimands using EDPS2, utilizing the same intercurrent event strategy as Supplementary estimand 1 for the primary endpoint.
[2] These endpoints will also have secondary supplementary estimands using EDPS6, utilizing the same intercurrent event strategy as Supplementary estimand 5 for the primary endpoint.
[3] The score at each visit is calculated as the mean daily score for the 7 days prior to and including the visit date. At least 4 daily scores must be available for the score at the relevant visit to be considered evaluable.
[4] Only for participants with relevant score ≥2 or ≥4 (as applicable) at baseline
[5] Evaluated for Weeks 1-4, 5-8, 9-12 and 13-16 and for Weeks 1-16.
[6] Evaluated for Weeks 1-8 and 9-16 and for and Weeks 1-16.

11.3.3. Exploratory Efficacy Estimands

Exploratory estimands will use the same intercurrent event strategy as the primary estimand, i.e., they will use the FAS and EDPS1 to give a composite strategy for the intercurrent event of topical

corticosteroid rescue therapy use <28 days before the evaluable timepoint and study discontinuation due to reasons relating to study medication and be estimated without regard to treatment compliance, any changes in background or rescue therapy or unblinding.

Exploratory estimands will be evaluated at all timepoints at which the relevant endpoints are collected.

Table 11-3: Exploratory Estimand Details

Data Type	Endpoint	Population Summary Measure of Interest
Continuous	Change and percentage change from Screening in EASI score Change from baseline in each of the SF-12 MCS and PCS scores Change from baseline in the ADCT scores Change from baseline in eosinophils and immune protein markers Change from baseline in immune cell RNA profile Change from baseline in PP-NRS score[1] Change from baseline in SD-NRS score[1]	Mean value in each treatment group
Time to event (1)	Time to first achievement of EASI-50 Time to first achievement of IGA of 0 or 1 with a ≥2 point improvement from baseline Time to first achievement of sustained EASI-50[2]	Cumulative proportion to have achieved the event at each visit
Time to event (2)	Time to first achievement of a ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline Time to first achievement of a sustained[3] ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline Time to first achievement of a ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline Time to first achievement of a sustained[3] ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline Time to first achievement of a ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline Time to first achievement of a sustained[3] ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline	Kaplan-Meier estimates of proportion of responders at each week from 1 to 16.
Response (1)	IGA of 0 or 1 with a ≥2 point improvement from screening Improvement of ≥2 and ≥4 points in PP-NRS score from baseline[1] Improvement of ≥4 points in SD-NRS score from baseline[1]	Proportion of responders at each timepoint
Response (2)	Development of skin infection requiring topical or systemic antibiotic treatment by Week 16	Proportion reporting at least one infection on or before the Week 16 visit.

[1] Evaluated daily from Day 2 to 112.
[2] Sustained EASI-50 is a response which is seen at least 2 consecutive visits.
[3] Sustained PP-NRS or SD-NRS improvement is defined as the relevant improvement shown at all evaluable days within at least a 14-day period.

The primary and selected secondary response endpoints relating to EASI, IGA and PP-NRS endpoints will be used in exploratory estimands which compare those who received topical corticosteroid rescue medication within specific windows with those who used no topical corticosteroid rescue therapy. These estimands will use all data as collected with no imputation for intercurrent events.

For Cohort 4 only, the primary and secondary endpoints relating to EASI, IGA, IGA*BSA and PP-NRS (those endpoints flagged in Table 11-3 for the use of secondary supplementary estimands) will also be used for exploratory estimands which compare the Cohort 1 EDP1815 treatment group with the Cohort 4 EDP1815 treatment group.

11.3.4. Safety Estimands

All safety estimands will use the safety analysis set. A treatment policy approach will be used for all safety estimands, including all data collected regardless of treatment discontinuation, treatment compliance, changes in background or rescue therapy or unblinding of the subject.

SDPS1 will be used to estimate safety endpoints which are collected at scheduled visits.

SDPS2 will be used to estimate safety endpoints which are assessed at any time in the study.

Table 11-4: Safety Endpoint Details

Data Point Set	Endpoint	Population Summary Measure of Interest
SDPS1	Change from baseline in vital signs Change from baseline in ECG parameters Change from baseline in clinical laboratory parameters Change from baseline in physical examination findings	Summary statistics at each visit for each treatment group
SDPS2	Adverse events and serious adverse events Worst-case change from baseline with respect to potentially clinical important criteria for vital signs, QTcF and clinical laboratory parameters Worst-case change from baseline with respect to values outside the normal ranges for vital signs, ECG parameters and clinical laboratory parameters	Incidence in each treatment group

11.4. Planned Analyses

For all Cohort 1-3 analyses, data for the relevant endpoint will be analyzed within the same model and the Cohort 1-3 placebo groups will be pooled.

For all Cohort 4 analyses, the Cohort 4 EDP1815 data will be compared to the Cohort 4 Matched Placebo data. In separate models for the primary and selected secondary endpoints, the Cohort 1 EDP1815 data will be added to the model and compared to the Cohort 4 EDP1815 data; these analyses will be considered as exploratory.

11.4.1. Analysis of Primary Estimand

The primary estimand will be analyzed using a logistic regression with parameters for treatment group, baseline IGA score and baseline EASI score.
Body mass index, gender, race, and region will also be considered and included in the model if found to be significant.

The actual and predicted probability of EASI-50 response in each treatment group together with the estimated odds ratios and associated confidence intervals for each treatment difference will be displayed together with p-values for the comparisons of active treatment vs pooled placebo.

Actual and predicted probabilities of EASI-50 at Week 16 for each treatment group will be plotted.

11.4.2. Analysis of Supplementary Estimands on the Primary Objective

The four supplementary estimands defined for the primary objective will be analyzed in the same manner as the primary estimand.

For the potential covariates of body mass index, gender, race and region: those covariates found to be significant in the primary analysis will be included in all models regardless of significance in order to ensure comparability of the models.

11.4.3. Cohort 4 Sensitivity Analysis of the Primary Estimand

A Bayesian dynamic borrowing method using a commensurate prior will be used for the placebo comparator in the primary analysis model, utilizing all Cohort 4 data and Cohort 1-3 placebo data (Hobbs, Carlin, Mandrekar, & Sargent, 2011). In contrast to the primary analysis method, this sensitivity analysis will borrow information from the Cohort 1-3 placebo patients dependent on the similarity in outcomes between the Cohort 4 and Cohorts 1-3 placebo groups further sensitivity analyses for the primary and secondary endpoints may also be performed on the Cohort 4 data either using the same dynamic borrowing methodology or using the Cohort 4 only placebo group as the comparator. Full details are provided in the SAP.

11.4.4. Analysis of Secondary Estimands

Continuous secondary estimands will be analyzed using a mixed model for repeated measures (MMRM) with parameters for treatment group, visit, baseline IGA score and relevant baseline score and the interaction for treatment*visit.

For the potential covariates of body mass index, gender, race and region: those covariates found to be significant in the primary analysis will be included in all models regardless of significance in order to ensure comparability of the models.

Least squares mean estimates and their 95% confidence intervals (CI) will be presented for the endpoint value at each visit. Treatment differences between each EDP1815 group and the pooled placebo group will be estimated using LS mean differences, 95% CI and p-values. Pairwise treatment differences between EDP1815 groups will be estimated with LS mean differences and 95% CI.

Least square mean (95% CI) estimates will be plotted against visit. Least square mean (95% CI) treatment differences between each EDP1815 treatment group and the pooled placebo group will also be plotted against visit.

Response estimands will be analyzed with a generalized linear mixed effects model with a logit link function. Treatment, visit, baseline IGA and the appropriate baseline questionnaire score will be included as parameters together with the treatment*visit interaction. Odds ratios with 95% CIs and p-values for each EDP1815 group compared to the relevant pooled placebo group at each visit will be presented. Odds ratios and 95% CIs will be presented for any comparisons between two EDP1815 treatment groups.

In the event that there are no responders in one of the treatment groups at a visit, data from that visit will be excluded from the model and only summary statistics will be produced showing the number and percentage of responders at that visit.

Count estimands will be analyzed with a Poisson regression model fitted with treatment and baseline IGA as covariates. An offset of log (days in study) will also be included in the model to account for any data from participants who withdrew early from the study. If the distribution of the count data suggests over-dispersion and/or zero inflation, then other models including the negative binomial or zero-inflated Poisson model may be considered.

Model estimated event rates and their 95% confidence intervals will be presented for each treatment group. Rate ratios with 95% CIs and p-values for each EDP1815 group compared to the relevant pooled placebo group at each visit will be presented. Rate ratios and 95% CIs will be presented for any comparisons between two EDP1815 treatment groups.

11.4.5. Analysis of Exploratory Estimands

Exploratory endpoints will be summarized only. No inferential analysis is planned.

For the daily PP-NRS and SD-NRS endpoints which are evaluated daily only graphical summaries will be presented.

For the time to first response endpoints for the PP-NRS and SD-NRS scores, participants who have not met the response definition before the Week 16 visit will be censored at the Week 16 visit, or at the time of withdrawal from the study for those who withdrew before Week 16.

For the time to sustained response endpoints for the PP-NRS and SD-NRS scores, it will not be possible for participants to start a sustained response less than two weeks before the Week 16 visit. Therefore, such participants will be censored at 14 days before the date of the Week 16 visit or at the time of treatment withdrawal for participants who do not complete the 16-week treatment period.

For the primary and secondary responder endpoints relating to EASI, IGA and BSA, summaries will be provided comparing the number and percentage of participants in each treatment group who respond at Week 16 between the following 4 subgroups:

- Participants with no rescue therapy use
- Participants with no rescue therapy use after the Week 4 visit
- Participants with no rescue therapy use after the Week 8 visit
- Participants with no rescue therapy use within 4 weeks of the Week 16 visit
- Participants with no rescue therapy use within 2 weeks of the Week 16 visit
- Participants with rescue therapy use within 4 weeks of the Week 16 visit
- Participants with rescue therapy use within 2 weeks of the Week 16 visit

For these endpoints, all participants who have Week 16 data available for the relevant endpoint will be included and there will be no imputation for any intercurrent events.

For the Cohorts 1-3 analyses, pairwise treatment differences between two EDP1815 treatment groups will be estimated as part of the modelling done for the primary and secondary analyses, but such estimates will be considered as exploratory.

For the Cohort 4 analyses of the primary and selected secondary estimands, separate models will be used which include the EDP1815 $1.6x10^{11}$ (Cohort 1) treatment group in addition to the Cohort 4 EDP1815 $8.0x10^{10}$ group and the Cohort 4 Matched Placebo group. From these tables, pairwise treatment differences between the two active EDP1815 groups will be estimated, with all such estimates being considered as exploratory.

11.4.6. Analysis of Safety Estimands

All safety data will be summarized by treatment group using the safety set and the data point set appropriate for the endpoint type.

11.4.7. Other Analyses

Tabulations will be provided for completion/withdrawal status, protocol deviations, study populations, demographic and other baseline characteristics, use of concomitant medications, and exposure to and compliance with IMP and emollients.

11.5. Handling of Protocol Deviations

Protocol deviations will be logged within the clinical trial management system and categorized dependent on the type of deviation and its significance.

Protocol deviations relating to the use of prohibited medications, to non-compliance with study treatment (including non-compliant emollient use) and to unblinding of the study before database lock will be accounted for as intercurrent events in the primary analysis.

11.6. Handling of Dropouts or Missing Data

Unless otherwise specified, missing data will be considered as missing at random and will be accounted for using mixed models for repeated measures, with all time points collected for the relevant endpoint included in the model.

Otherwise, missing data will not be imputed.

11.7. Planned Interim Analysis and Data Monitoring

An interim analysis may be undertaken prior to the end of recruitment for Cohorts 1,2 and 3. The purpose of this interim analysis is to check the sample size assumptions for placebo response rates and drop-out rates.

The balance of participants enrolled to each treatment group will also be checked during this analysis. Due to the use of stratification by IGA at baseline at both the cohort and treatment-within-cohort level, there may be up to 9 incomplete blocks of treatment assignments remaining at the end of randomization. This may lead to imbalance between the cohorts and/or treatment groups. An unblinded team within the Biostatistical Vendor will review the overall numbers of participants randomized to each treatment group and as a result may specify to the IRS Vendor that the randomization numbers for an individual cohort and/or the randomization numbers for an

individual treatment within a cohort are restricted and no longer available for use for the remaining participants to be randomized. The aim of this will be to ensure that each of the four treatment groups has a minimum of 73 randomized participants.

Blinded analyses of eCOA data will be performed during the recruitment period. As a result of these, possible changes in the conduct of the study may be to stop recruitment from one or more of the baseline IGA severity strata. No other changes to study conduct are expected.

The data for Cohorts 1, 2 and 3 will be locked, unblinded and analyzed before the end of Cohort 4.

11.8. Determination of Sample Size

Cohorts 1-3

The sample size was calculated using the assumption that data from the placebo participants in the three cohorts can be pooled prior to comparison with the EDP1815 treatment groups. No adjustments for multiple testing have been made.

The primary efficacy endpoint is the achievement of EASI-50 at Week 16. The pooled placebo response rate is estimated to be approximately 25% and a doubling of this to 50% for EDP1815 would be considered as clinically meaningful.

Using a two-sided test at the 5% level of significance, 58 participants in each treatment group would give 80% power to detect a difference in one of the EDP1815 cohorts compared to the pooled placebo group. There would also be more than 90% power to compare the pooled EDP1815 6.4 $x10^{11}$ daily dose or all the EDP1815 group to the pooled placebo group.

Under the assumption of a 20% drop-out of participants prior to Week 16 this will require a total of at least 73 participants to be enrolled in each treatment group. In order to allow for the 3:1 randomization in each cohort this has been adjusted to 75 participants per treatment group to give a total of 300 participants recruited. With 75 EDP1815 participants and 25 placebo participants in each of the three cohorts.

Cohort 4

Using the same assumptions relating to the placebo rate, clinically meaningful difference, significance level, and drop-out rate as above for Cohorts 1-3, approximately 70 participants are required in each of the EDP1815 $8.0x10^{10}$ and Cohort 4 Matched Placebo groups to provide approximately 80% power in detecting a difference between EDP1815 and placebo in Cohort 4.

In order to allow 50% of the placebo control group to be concurrent controls and 50% to be historic matched controls from Cohorts 1-3, a 2:1 randomization will be used to enroll 70 EDP1815 $8.0x10^{10}$ subjects and 35 placebo participants to Cohort 4.

If sensitivity analyses indicate that pooling of the Cohort 4 placebo group with the Cohort 1-3 matched placebo data is inappropriate, then the power of the comparison between the Cohort 4

EDP1815 and placebo groups is approximately 65% if only Cohort 4 placebo participants could be used in the treatment comparisons.

12.ETHICS AND REGULATORY REQUIREMENTS

12.1. Informed Consent

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the Informed Consent Form (ICF) should be signed and personally dated by the participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or medically licensed Sub-Investigator). The participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. Study specific procedures may not be performed for a given participant, without having obtained his/her written consent to participate in the study.

12.2. Participant Identification Cards

Upon signing the Informed Consent and Assent Form(s) (as applicable), the participant or legal representative will be provided with a participant identification card in the language of the participant. The Investigator will fill in the participant identifying information and medical emergency contact information. The Investigator will instruct the participant to keep the card with him/her at all times.

12.3. Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator and Sponsor or their designee will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable

country--specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator or the Sponsor or their designee will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant--related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

The Sponsor (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

12.4. Participant Privacy

The Sponsor or their designee will protect the participant's confidentiality. Throughout this study, all data forwarded to the Sponsor or their designee, will be identified only by the participant number assigned at the Screening Visit and/or Day 1 Visit. All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in accordance with applicable data protection law.

The Investigator agrees that representatives of the Sponsor, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

12.5. Protocol Amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective. Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by the Sponsor, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

12.6. Insurance

Insurance coverage will be handled according to local requirements.

12.7. Financial Disclosures

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

12.8. Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior written authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

12.8.1. Dissemination of Clinical Study Data

The Sponsor and the Investigator are committed to publish data in accordance with applicable regulations and transparency guidance. Results will be published within 2 years of finalization of the CSR and will only be delayed to the second year if earlier publication may be detrimental to the financial position or intellectual property rights of the Sponsor.

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14.APPENDICES

14.1. Hanifin and Rajka (1980) Criteria for Diagnosis of Atopic Dermatitis

From Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;92 (Suppl):44-47.

Major Features: must have 3 or more of the following:

1. Pruritus
2. Typical morphology and distribution:
    a. Flexural lichenification or linearity in adults
    b. Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Features: plus 3 or more of the following:

1. Xerosis
2. Ichthyosis / palmar hyperlinearity /keratosis pilaris
3. Immediate (type 1) skin-test reactivity
4. Raised serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (especially Staph. aureus and Herpes simplex) or impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor / facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental / emotional factors
23. White dermographism / delayed blanch

14.2. Classification of Potency of Topical Corticosteroids

Potency	Class	Topical Corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream 0.05%
		Diflorasone diacetate	Ointment 0.05%
High	II	Amcinonide	Ointment 0.1%
		Betamethasone dipropionate	Ointment 0.05%
		Desoximetasone	Cream or ointment 0.025%
		Fluocinonide	Cream, ointment or gel 0.05%
		Halcinonide	Cream 0.1%
	III	Betamethasone dipropionate	Cream 0.05%
		Betamethasone valerate	Ointment 0.1%
		Diflorasone diacetate	Cream 0.05%
		Triamcinolone acetonide	Ointment 0.1%
Moderate	IV	Desoximetasone	Cream 0.05%
		Fluocinolone acetonide	Ointment 0.025%
		Fludroxycortide	Ointment 0.05%
		Hydrocortisone valerate	Ointment 0.2%
		Triamcinolone acetonide	Cream 0.1%
	V	Betamethasone dipropionate	Lotion 0.02%
		Betamethasone valerate	Cream 0.1%
		Fluocinolone acetonide	Cream 0.025%
		Fludroxycortide	Cream 0.05%
		Hydrocortisone butyrate	Cream 0.1%
		Hydrocortisone valerate	Cream 0.2%
		Triamcinolone acetonide	Lotion 0.1%
Low	VI	Betamethasone valerate	Lotion 0.05%
		Desonide	Cream 0.05%
		Fluocinolone acetonide	Solution 0.01%
	VII	Dexamethasone sodium phosphate	Cream 0.1%
		Hydrocortisone	Lotion, cream, or ointment 2.5%
		Hydrocortisone acetate	Cream 1%
		Methylprednisolone acetate	Cream 0.25%

Source: WHO (1997) and Tadicherla et al 2009

14.3. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Child-Bearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal

2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Documented bilateral tubal ligation

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months prior to the Screening Visit without an alternative medical cause. In the absence of 12 months of amenorrhea, postmenopausal women will be assumed to be WOCBP and will need to follow contraceptive guidance and have pregnancy tests performed throughout the course of the study per the Schedule of Activities (SOA).

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study.

Contraception Guidance

Male participants with a female partner of child-bearing potential must either

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Use a male condom during each episode of penile penetration during their participation in the study and for 90 days after the last dose of IMP.

- Have a confirmed vasectomy.

In addition, all male participants must refrain from donating sperm for the duration of the study and for at least 90 days following their last dose.

Female participants
Female participants of child-bearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 14-1 below.

Table 14-1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b]. • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b]. • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention, including at least 1 complete menstrual cycle (cycle (≥ 30 days) for women and 90 days for men post last dose. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, a highly effective method of contraception plus condoms should be utilised during their participation in the study up to and including at least 1 complete menstrual cycle (≥ 30 days) for women and 90 days for men post last dose.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative pregnancy test.
- Pregnancy testing is required at screening.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies to all male participants who receive EDP1815.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related- SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 9.5 **Reporting Serious Adverse Events**. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

14.4. EDP1815 COVID-19 Risk Assessment

Antiviral responses are activated rapidly after viral infection in order to control and prevent dissemination of the virus. Virus infection results in two general types of immune response. The first is a rapid-onset innate immune response against the virus, which involves the synthesis of Type 1 interferons and the stimulation of Natural Killer (NK) cells. If the infection proceeds beyond the first few rounds of viral replication, the innate immune response will trigger the adaptive immune response. The adaptive immune response itself has two components, the humoral response (the synthesis of virus-specific antibodies by B lymphocytes) and the cell-mediated response (the synthesis of specific CD8+ cytotoxic T lymphocytes that kill infected cells). Both of these components of the adaptive immune response result also in the production of long-lived memory cells that allow for a much more rapid response to a subsequent infection with the same virus. Thus, an immune competent host should be able to mount both an innate and adaptive immune response.

EDP1815 is a single strain of human commensal *Prevotella histicola* that is being clinically tested to treat inflammatory skin diseases such as psoriasis and atopic dermatitis (studies 1815-101, 1815-201, and 1815-207); in a pharmacodynamic immune challenge study to Keyhole Limpet Haemocyanin (KLH) (study 1815-102); and also to treat the complications of infection with COVID-19 (study 1815-204 and 1815-205). EDP1815 is administered orally and is gut-restricted. Therefore, EDP1815 exerts its anti-inflammatory effects on peripheral tissue through engagement of cells of the intestine, including small intestinal epithelial cells and immune cells in the lamina propria.

EDP1815 has been shown in preclinical mouse inflammation models to reduce antigen-specific T cell responses, without impacting:

- The anti-viral TLR3-mediated Type 1 interferon (alpha and beta) response
- Interferon-gamma production by T cells and NK cells
- Immune cell subsets (absolute number and percentage), including CD8 T lymphocytes, B lymphocytes, and myeloid lineage cells
- The antigen-specific antibody responses (IgM and IgG)

In human immune cell in vitro assays, EDP1815 did not alter the ability of human dendritic cells to induce the production of interferon-gamma from memory CD8 T cells in response to a viral peptide pool (Cytomegalovirus, Epstein-Bar virus, and Influenza virus), an important component of an anti-viral response.

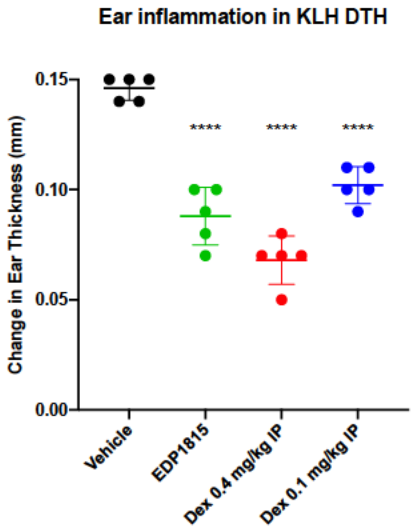
And clinically, treatment with EDP1815 was shown to reduce specific inflammatory myeloid cell cytokines such as IL-6 and IL-8, while not affecting levels of T cell cytokines such as interferon-gamma, produced by circulating peripheral blood mononuclear cells.

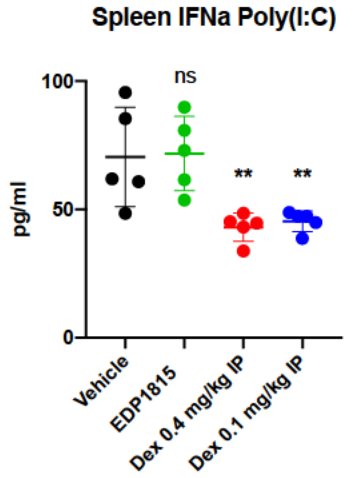
Taken together, the data demonstrate that treatment with EDP1815 does not result in general immuno-suppression of multiple immune pathways but is effective through a selective restoration of immune homeostasis.

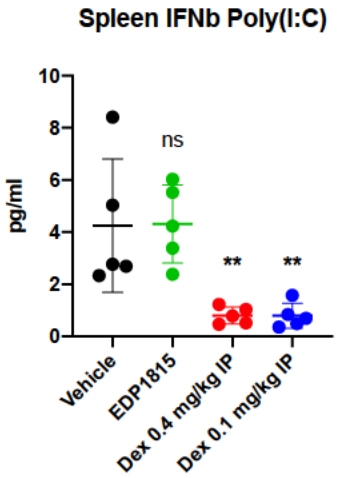
TLR3-mediated induction of Type 1 interferons in the KLH delayed-type hypersensitivity model

Mice were immunized by subcutaneous injection with KLH emulsified with Complete Freund's Adjuvant. On Day 6 after the sensitization, mice were dosed for 3 days with oral EDP1815 or dexamethasone given intraperitoneally. On day 8, mice were challenged by intradermal ear injection with KLH. The DTH response was evaluated 24 hours post-challenge. For the ex vivo cytokine analysis, spleen cells from treated mice were incubated for 48 hours in vitro and stimulated with polyinosinic-polycytidylic acid (poly I:C), a molecule that mimics viral double-strained RNA, and a potent ligand for Toll-like receptor 3, which induces interferon-alpha and interferon-beta from immune cells.

Results: Three days of dosing with EDP1815 or dexamethasone significantly inhibited ear inflammation. In addition, while dexamethasone significantly inhibited the production of interferon-alpha and interferon-beta in the spleen cell stimulation assay, oral EDP1815 had no impact on these Type 1 interferons. This demonstrates that EDP1815 selectively inhibits tissue inflammation while preserving protective Type 1 interferon responses.

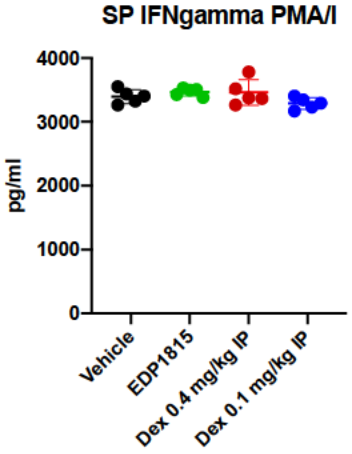






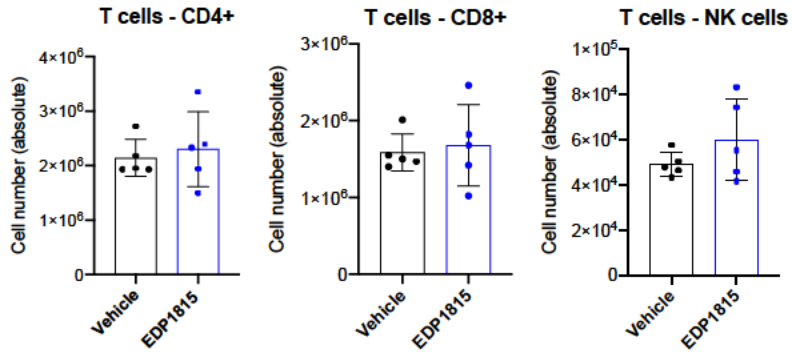
Interferon-gamma production by lymphocytes in vivo

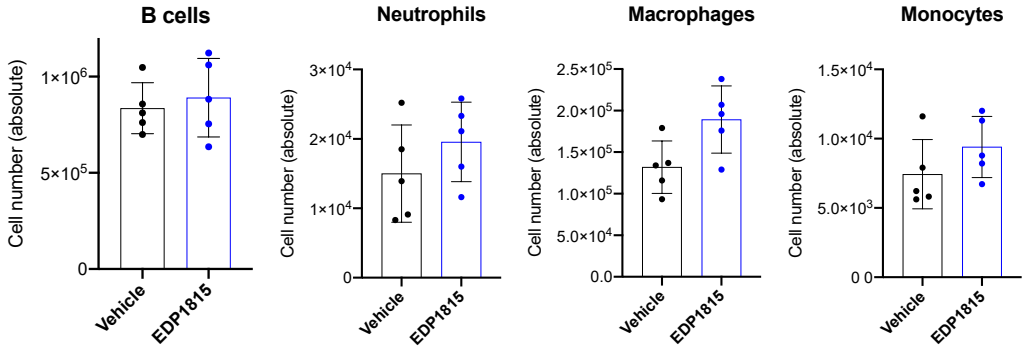
In the same study, spleen cells were restimulated with PMA and ionomycin. PMA activates protein kinase C, while ionomycin is a calcium ionophore, and stimulation with these compounds bypasses the T cell membrane receptor complex and will lead to activation of several intracellular signaling pathways, resulting in T cell activation and production of a variety of cytokines. Stimulation with PMA/ionomycin induced robust production of interferon-gamma from spleen cells, and treatment with EDP1815 or dexamethasone did not reduce the production of interferon-gamma, demonstrating that the Cytotoxic CD8 T cell/NK axis of immunity was intact.



Immune cell subsets quantification after EDP1815 dosing

In other DTH studies, immune cell numbers in lymphoid tissues were measured. Mesenteric lymph nodes which drain the small intestine were removed at the end of a delayed-type hypersensitivity study, performed as described above. Single cell suspensions were made from the lymph nodes, stained using antibodies against cell surface markers, and quantified by flow cytometry. Treatment with EDP1815 for 5 days did not alter any immune cell subsets, including T cells, NK cells, B cells, neutrophils, macrophages, and monocytes in the lymph nodes.



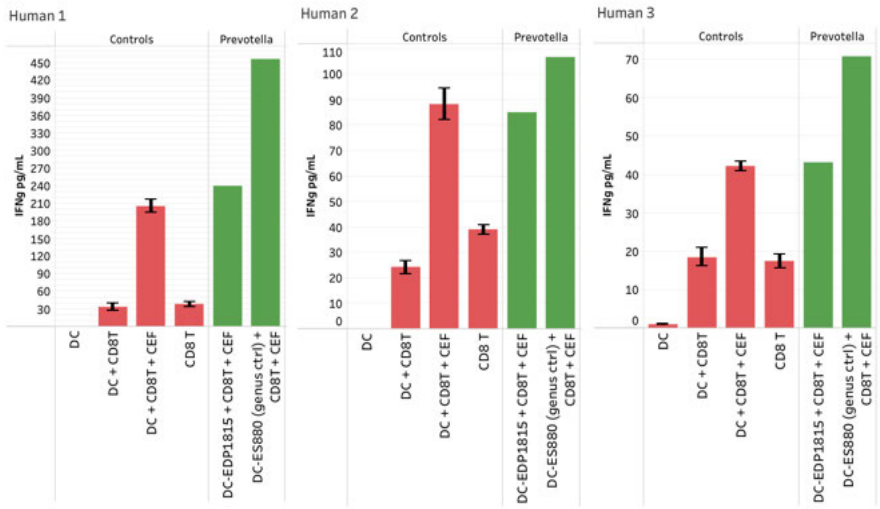


KLH-specific antibody response

Antibodies are one of the essential features of antigen-triggered adaptive immunity against viruses and requires a coordinated response between antigen-presenting cells such as dendritic cells, antigen-specific helper T cells, and antigen-specific B cells. Although treatment with EDP1815 causes a marked reduction in peripheral inflammation in the KLH delayed-type hypersensitivity model, no effect on KLH-specific IgM or IgG has been observed in either preclinical models or in a clinical study (data not shown).

In vitro assay co-culture with human dendritic cells and CD8 T cells

An in vitro assay with primary human DCs and autologous CD8+ T cells was carried out to measure the capacity of EDP1815 to modulate antigen-specific CD8+ T cell responses. Briefly, primary human DCs from 3 healthy donors were differentiated in vitro for 7 days. To assess the immuno-modulatory properties of EDP1815, DCs were incubated with EDP1815 or ES880, a different *Prevotella* strain that does not exhibit anti-inflammatory activity, for 24 hours in vitro. After 24 hours of microbe conditioning, microbes were removed from the DC culture and autologous human CD8+ T cells and CEF Class I peptide pool was added. The CEF peptide pool is composed of peptides from Cytomegalovirus, Epstein Bar virus, and Influenza virus, pathogens to which the majority of the human population has been exposed. After 24 hours of stimulation with CEF peptide, DC-CD8+ T cell supernatants were collected and IFNγ was measured. When human DCs were incubated with EDP1815, the IFNγ response to CEF was not affected (neither enhanced nor decreased) compared to the DC-CD8 T cell co-culture control. In contrast, incubation with ES880 led to increased production of IFNγ.



Conclusion

The combination of in vitro, in vivo, and ex vivo data demonstrate that EDP1815 does not broadly impair either innate or adaptive immune responses. EDP1815 is orally delivered and gut restricted, and therefore its effect is exerted through local interactions with cells of the small intestine, which are then translated from the gut to the periphery to resolve inflammation. Anti-viral responses such as cytotoxic T cell production of interferon-gamma, innate anti-viral production of interferon-alpha and interferon-beta, and the generation of high affinity antibodies are all preserved after treatment with EDP1815.

The data demonstrate that treatment with EDP1815 results in resolution of multiple pathways of inflammation without leading to immunosuppression of the host response.

14.5. Toxicity Grading Scale

The following scales come from the FDA Guidance for Industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*, September 2007.

Temperature Adverse Event Grading Scale

Vitals Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (ºC)** (ºF)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 - 104	> 40 >104

Laboratory Results Adverse Event Grading Scale

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

15. DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice (GCP) and local laws and requirements.

I will ensure that all Sub-Investigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by the Sponsor, Evelo Biosciences, Inc.

All rights of publication of the results reside with the Sponsor, Evelo Biosciences, Inc, unless other agreements were made in a separate contract.

_____

Signature of Investigator Date

_____

Investigator Name

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City)

16.SPONSOR DECLARATION

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical protocol in addition to the following:

- Ethical principles originating from the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 and Good Clinical Practice (GCP).
- All applicable laws and regulations including data privacy laws and regulations.

Sponsor Signatories:

[redacted]

Date

[redacted]

Date

[redacted]

Date

[redacted]

Date

17.PROTOCOL AMENDMENTS

Document	Protocol Version	Date	Type of Protocol Amendment
Amendment 4	5.0	25 April 2022	Global (substantial)
Amendment 3	4.0	29 November 2021	Global (substantial)
Amendment 2	3.0	07 October 2021	Global (substantial)
Amendment 1	2.0	13 September 2021	Global (substantial)
Original Protocol	1.0	30 June 2021	Not Applicable

Protocol Amendment 4, Protocol Version 5.0, Dated 25 April 2022

The study protocol has been amended to include an additional cohort (Cohort 4) which will run once Cohorts 1, 2 & 3 have completed enrollment. The dose for Cohort 4 is 1 capsule, once daily (0.8×10^{11} cells). Study EDP1815-201 has now shown no evidence of a dose response over 16 weeks of dosing in psoriasis (doses of 0.8×10^{11}, 3.2×10^{11}, and 8.0×10^{11} total cells once daily), therefore, one capsule once daily is our anticipated Phase 3 dosing regimen in psoriasis and atopic dermatitis. Additionally, for Cohorts 1, 2, & 3, two capsules enables a more scientifically sound comparison between once daily and twice daily dosing, and also permits comparison of different manufacturing processes at the same capsule load.

Major changes are summarised below and have been made throughout the protocol, where appropriate.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section no. and name	Description of change	Brief rationale
1.2 Previous Experience with EDP1815 and Rationale for Treating Atopic Dermatitis	Paragraph describing number of participants exposed to EDP1815 was updated to reflect most recent data.	Data is from January 2021 and is currently outdated.
2.1 Primary Objectives	Following estimand approach was added to the protocol: • *Using an alternative composite strategy for topical corticosteroid rescue therapy, with all participants who use any topical corticosteroid therapy at any time between Day 1 and Week 16 considered*	This was added to ensure that Evelo has an estimand approach which matches that of our competitors.

	as non-responders at the Week 16 visit.	
2.3 Exploratory Objectives 4.3 Exploratory Variables	Following exploratory objective was added to the protocol: • *To evaluate the effect of early use of rescue therapy on Week 16 responder status.* Additionally, exploratory variables were updated to include the following: • *To evaluate the effect of early use of topical corticosteroid rescue therapy on Week 16 responder status, the subgroup of participants with no rescue use at any time before Week 16 will be compared to subgroups of participants with rescue therapy use within only the first 4, 8, 12 and 14 weeks prior to the Week 16 visit. For these subgroups, the following endpoints will be summarized: Percentage of Participants Achieving EASI-50, EASI-75 and EASI-90.* • *Percentage of Participants Achieving IGA 0 or 1, with and without a 2-point improvement from Baseline* • *Percentage of Participants Achieving BSA-50 and BSA-75*	This was added to help Evelo evaluate our estimand approach for Phase 3.
Protocol Summary 2.1 Primary Objectives 4.1 Study Description 4.3 Planned Number of Participants 4.6 Schematic Study Design 4.7. Rationale for study design and selection of dose 6.1 Investigational Medicinal Product(s) Table 6-1: IMP to be Administered	Added Cohort 4 and made corresponding changes to number of participants, ratio and regimen, and cohort description throughout, and statistics section, as required.	See rationale above.

11. Statistics		
4.5 Schedule of Study Assessments 7.1 Screening Visit 7.2 Day 1 Visit 9.11.4 Microbiome Sample	Removal of fecal sample requirement for those participants that enroll under Protocol Version 5.0.	Enough samples have been collected thus far for required microbiome analyses.
5.1 Inclusion Criteria	Inclusion criterion #4 update to clarify IGA caps. The bolded, underlined text was added to this criterion: *7. Have severity of atopic dermatitis meeting the below criteria at both Screening and Day 1:* *i. An IGA of 2, 3 or 4 on the vIGA scale, and;* *ii. A BSA of ≥5%, and;* *iii. An EASI score of ≥6.* ***A cap will be set for each of the three IGA severity grades. When this cap is reached, Sponsor will notify sites and participants with severity score at Screening and/or Day 1 matching the closed stratum should be considered ineligible according to Inclusion Criterion 4i. See Section 11.7 Planned Interim Analysis and Data Monitoring.***	Changes were made to inclusion criterion #4 in order to allow for a cap
5.2 Exclusion Criteria	Exclusion criterion #20 changed from the strikethrough text to the **bolded, underlined** text below: 20. *Active untreated mental or psychiatric disorder. Participants who are on stable dosing of medication for a mental or psychiatric disorder for at least 6 months before signing of ICF and whose treating physicians consider them to be mentally stable may be enrolled.* Change to: ***20. Active mental or psychiatric disorder, which, in the opinion of the Investigator or***	Changes were made to exclusion criterion #20 in order to allow physician judgement of inclusion of participants with an untreated mental or psychiatric disorder in the study.

	Sponsor, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study. Exclusion criterion #23 updated to remove the strikethrough text and include the bolded, underlined text: *23. Treatment with another investigational drug or device within 3 months ~~of signing the ICF~~ or 5 half-lives of investigational agent, **prior to randomization** whichever is longer.*	Changes were made to exclusion criterion #23 in order for the language regarding timing to be consistent with other exclusion criteria.
6.1 Investigational Medicinal Product(s)	Description of EDP1815 enteric-coated capsules updated to include Cohort 4 drug substance description and manufacturing details.	Cohort 4 added to study protocol.
9.12.3 12-Lead Electrocardiogram	The following, strikethrough text was removed from this section: *A single 12-lead electrocardiogram (ECG) will be obtained at specified visits using an ECG machine that automatically calculates heart rate and measures PR, RR, QRS, QT and QTcF (Fridericia) intervals. ~~If the ECG machine does not calculate QTcF, this will be calculated by the site and entered into the CRF.~~*	Electronic Data Capture (EDC) calculates QTcF intervals as a derived field.
10.2.1 Definition of Source Data	The following **bolded, underlined** text added to this guidance: *The following data will be considered as electronic source and therefore, will not be recorded directly into the EDC and will not appear in a separate source document as defined above, **unless there is a circumstance, such as a global power outage, making it difficult for site staff to collect this data electronically.** Any information about a participant that is collected during this study will remain secured and confidential and will be handled per applicable regulations (i.e., data collected via mobile applications).*	Text added to ensure that data is not missed and is collected at a minimum via paper when electronic means are not possible due to unforeseen circumstances.

14.3 Contraceptive Guidance and Collection of Pregnancy Information	The following **bolded, underlined** text added to this guidance: *Women in the following categories are not considered WOCBP:* *4. Premenarchal* *5. Premenopausal female with 1 of the following:* • *Documented hysterectomy* • *Documented bilateral salpingectomy* • *Documented bilateral oophorectomy* • ***Documented bilateral tubal ligation***	To further clarify that women with documented bilateral tubal ligation are not considered WOCBP and may be considered for enrollment in the study without the use of additional contraception.

Protocol Amendment 3, Protocol Version 4.0, Dated 29 November 2021

The study protocol has been amended to include a lower dose to increase the range of doses being tested to help understand the lower part of the dose response curve. Major changes are summarised below and have been made throughout the protocol, where appropriate.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section no. and name	Description of change	Brief rationale
Protocol Summary 4.1 Study Description 4.7.2 Dose Rationale 6.1 Investigational Medicinal Product(s) Table 6-1: IMP to be Administered	Cohort 1 total cell count changed from $3.2x10^{11}$ total cells at 1 capsule once daily to $1.6x10^{11}$ total cells at 2 capsules once daily. Distinction made that the lower dose IMP is derived from a separate process.	To explore and understand the lower part of the dose response curve.
4.1 Study Description	Removal of 'parallel run'.	Allows flexibility to run Cohorts based on availability of IMP.
4.1 Study Design 11.7 Planned Interim Analysis and Data Monitoring	Language clarified to allow for the check of sample size assumptions for placebo response and drop-out rates.	Made the reasons and scope for an interim analysis more explicit and allowed for this to be at any time prior to end of screening, rather than at a pre-specified recruitment point.
6.1 Investigational Medicinal Product(s)	Further clarification of placebo EDP1815 enteric-coated capsules.	Allows investigator's to further determine a participant's eligibility by ruling out potential allergies to IMP.
6.9.3 Immunizations	Language updated to reflect timing of IMP dosing with administration of vaccine.	Changes made to cover timing of any administration of the SARS-CoV-2 (COVID) vaccines as there are now booster vaccines available to the general public.
9.5 Reporting Serious Adverse Events	Language regarding reporting timelines for SAEs was updated to include the **bolded, underlined** text: *Serious Adverse Events (SAEs) must be reported to the Medical Monitor and Sponsor* ***immediately, without undue delay but no later than*** *within 24 hours of the site learning of the SAE.*	This language was updated to be aligned with the new EU Clinical Trials regulations that will come into effect 31 January 2022.

11.2 General Statistical Considerations 11.3.1 Primary Estimand and Supplementary Estimands of the Primary Objective 11.3.2 Secondary Estimands 11.8 Determination of Sample Size	Language amended to clarify how data will be pooled and compared across the 3 treatment cohorts.	The change to cohort 1 meant that the 'all EDP1815' vs placebo comparison was no longer appropriate as a primary analysis. In addition, the exploratory comparisons between EDP1815 groups required updating.
Table 11-1: Intercurrent Event Strategies for the Primary and Supplementary Estimands Table 11-2: Secondary Estimand Details	Estimands clarified and reordered throughout both tables.	Minor corrections to issues found since finalization of V3

Protocol Amendment 2, Protocol Version 3.0, Dated 07 October 2021

The study protocol has been amended to address comments raised by the FDA following their review of the Protocol Amendment, Protocol Version 2.0, dated 13 September 2021. Major changes are summarised below and have been made throughout the protocol, where appropriate.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section no. and name	Description of change	Brief rationale
9.4.1 Assessments of AEs	Language amended to further clarity how AEs will be collected.	Updated per the FDA's recommendation.
9.9 Study Halting Criteria	Language amended to further clarify the situations in which the study may be halted.	Amended per the FDA's recommendation.

Protocol Amendment 1, Protocol Version 2.0, Dated 13 September 2021

The study protocol has been amended to address comments raised by the FDA following their review of the original protocol, Protocol Version 1.0, dated 30 June 2021. Additional updates were made to address a change in primary endpoint and study treatment duration. Major changes are summarised below and have been made throughout the protocol, where appropriate.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section no. and name	Description of change	Brief rationale
Protocol Summary 2. Study Objectives 3. Study Variables 11. Statistics	Change in primary endpoint.	Proportion of participants achieving EASI-50 is a more clinically relevant and meaningful endpoint than the aggregated mean change in EASI across all participants, providing a better indication of the clinical utility of EDP1815.
Protocol Summary 2. Study Objectives 3. Study Variables 4. Study Design 4.5 Schedule of Study Assessments 4.6. Schematic Study Diagram 5.4 Discontinuation from Treatment and/or Withdrawal 6.2 Investigational Medicinal Product(s) to be Administered 6.3 Packaging 7. Study Procedures by Visit 8. Efficacy Assessments 11. Statistics	The overall study treatment duration was changed from 12 weeks to 16 weeks.	Increased probability of treatment benefit with EDP1815 with a longer treatment period. 16 weeks is an accepted duration of placebo-controlled study in atopic dermatitis.
Protocol Summary 4. Study Design 11. Statistics	Increase in overall enrollment from 264 to 300 participants.	Change in primary endpoint requiring new power calculation.

Protocol Summary 4. Study Design 4.6. Schematic Study Diagram	Change in number of participants per cohort: 75 participants per cohort will receive active IMP and 25 participants per cohort will receive placebo, for an overall study total of 225 participants receiving active and 75 participants receiving placebo.	Change in primary endpoint requiring new power calculation.
4.3 Planned Number of Participants	Increase in overall participating centers from 55 to 60.	Updated due to extension in study treatment duration and increase in overall enrollment.
4.5 Schedule of Study Assessments 4.6. Schematic Study Diagram 6.6 eDiary 7. Study Procedures by Visit 11. Statistics	An additional visit was added to the Schedule of Assessments for a total of 8 study visits over a 6-month period. Study visits are now Screening, Day 1, Week 2, Week 4, Week 8, Week 12, Week 16 and Week 20.	Updated due to extension in study treatment duration.
4.5 Schedule of Study Assessments 7. Study Procedures by Visit 9.13.1 Digital Photography	Digital photography language updated.	Additional photographs added to allow monitoring of entire skin surface, rather than just lesions present at the start of the study.
5.2 Exclusion Criteria	Exclusion criteria #2 updated to exclude all participants with prior exposure to EDP1815.	Alignment with other Evelo protocols
6.9.1 Permitted Concomitant Medications and Treatments 6.9.1.2. Rescue Therapy	Additional language added to allow antimicrobial therapy for secondary skin infections with permitted treatments listed. Language amended to allow rescue therapy throughout entire treatment period.	Addresses FDA hold item
9.4.1 Assessments of AEs	Language added to clarify how AEs will be solicited from the participant.	Addresses FDA hold item
9.4.2 Assessments of Severity of AEs	Language added to clarify that abnormal laboratory results that are found to be clinically significant adverse events will be graded according to the FDA Guidance for Industry Toxicity Grading Scale.	Added per the FDA's recommendation.