CLINICAL STUDY PROTOCOL

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A LONG-TERM EXTENSION TRIAL IN PARTICIPANTS WITH ATOPIC DERMATITIS WHO PARTICIPATED IN PREVIOUS PHASE 2 AND 3 EDP1815 TRIALS

PROTOCOL EDP1815-208

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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
EC	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
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment

IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LS	Least Squares Mean Estimate
mL	Milliliter
OLE	Open Label Extension
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
SLS	Sodium Lauryl Sulfate
SOP	Standard Operating Procedure
TCPD-1815	Total Cells per Day of EDP1815
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
WOCBP	Woman of Child-Bearing Potential

PROTOCOL SUMMARY

Study Objectives:

The primary objective of the study is to:

- Evaluate the long-term safety and tolerability of EDP1815 in the treatment of atopic dermatitis.

The secondary objective of the study is to:

- Evaluate the efficacy of long-term treatment with EDP1815 in the treatment of atopic dermatitis.

Primary endpoint: The incidence and rate per 100 patient-years of treatment emergent adverse events (TEAEs) during the 36-week treatment and 4-week follow-up period.

Secondary endpoints: The Eczema Area and Severity Index (EASI) Score will be utilized to measure the efficacy of EDP1815 in the treatment of atopic dermatitis. In addition to EASI, the Investigator's Global Assessment (IGA), percentage of Body Surface Area (BSA), Product of the IGA and BSA (IGA*BSA), the SCORing Atopic Dermatitis (SCORAD), the Dermatology Life Quality Index (DLQI), the Peak Pruritus Numerical Rating Scale (PP-NRS), the Sleep Disturbance Numerical Rating Scale (SD-NRS), the Patient Oriented Eczema Measure (POEM) and the Atopic Dermatitis Control Tool (ADCT) will be measured throughout the study.

The number of courses of treatment with rescue therapies; and with antibiotic treatment due to skin infection, per participant, will also be measured.

Brief Study Design: This is an Open-Label Extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of EDP1815 in participants with mild, moderate, and severe atopic dermatitis who have completed the treatment period of a prior clinical study ("parent study") with EDP1815. The parent study of this open label extension protocol is the EDP1815-207 study; 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. The EDP1815-207 study will be referenced as the parent study throughout the protocol.

This study may serve as an open label extension study for future EDP1815 studies in Atopic Dermatitis.

All participants in this study will be treated with EDP1815, regardless of the treatment assignment in the EDP1815-207 study. To minimize bias, during dosing in EDP1815-208, investigators and participants will continue to be blinded to participants' treatment allocation in the parent study whilst it is ongoing. Participants in this study will be treated with EDP1815 for up to 36 weeks, followed by a follow-up visit at approximately 4 weeks after the end of treatment.

Interim safety and efficacy analyses may be performed throughout the study as required for ongoing evaluation of the benefit-risk profile for EDP1815. These may include either all participants enrolled in the study or use of a subset of participants who transitioned to this study from a specific parent study. Interim analyses may also incorporate data collected within the parent Atopic Dermatitis EDP1815 studies which feed into this study.

Study Duration: The maximum study duration is up to 40 weeks for all participants, which will include a 36-week treatment period and a 4-week post treatment follow-up period. The participants may move directly from the parent study into the open label treatment phase without a break in study treatment, or within 7 days of completing the treatment period of the parent study. If the participants move directly into this study without a break in treatment from the parent study, the Day -1 visit should be performed at the same time as the end of treatment visit of the parent study.

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 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). Newer topical therapies for AD include Janus Kinase (JAK) and Phosphodiesterase 4 (PDE) inhibitors (Bieber, 2021). Unfortunately, there are associated issues with such current treatments including adverse effects, limitations in efficacy, and low patient acceptability and tolerability, particularly when used as chronic treatment options.

There are currently no licensed oral treatments for mild to moderate atopic dermatitis. There are currently two classes of oral medications approved for the treatment of moderate to severe atopic dermatitis; Ciclosporin (approved in the European Union (EU)) and JAK Inhibitors (newly

approved in the EU & US). Due to its associated risks and side-effects, such as renal failure, ciclosporin is generally only recommended for short-term use (Katoh, 2019). The most common serious adverse reactions associated with JAK inhibitors are infections, others include nausea, headache, and acne. 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 dupilumab and tralokinumab are now licensed as a biologic injectable treatment and are 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 experimental 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 Type-1 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 January 2022, a total of 458 adult participants have been exposed to EDP1815 in the phase 1 and 2 studies. The breakdown is as follows: phase 1 studies: 134 participants in EDP1815-101 (complete) and 24 healthy volunteers in EDP1815-102 (complete) and12 participants in EDP1815-104 (ongoing). In Phase 2 studies, approximately 166 participants have been exposed to EDP1815 for up to 16 weeks in duration in the EDP1815-201 Psoriasis study (complete), 8 participants in the EDP1815-205 COVID-19 study (complete) and 114 participants in TATIC-E (complete). To date, EDP1815 is well tolerated with a safety profile comparable to placebo and there are no AEs of special interest.

In the Phase 1b study (EDP1815-101), 16 participants with mild or moderate atopic dermatitis 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, IGA*BSA and SCORAD, as well as within the patient-reported outcomes, which also found improvements in itch and sleep scores. A further 16 participants were treated with EDP1815 daily for 8 weeks at a capsule dose of 6.4 x 10^{11} total cells, with another 8 participants on placebo in cohort 10 of this study. In this cohort, EDP1815 was shown to be well-tolerated with no treatment-related adverse events of moderate or severe intensity and no serious adverse events through eight weeks of dosing. The above efficacy was not clearly replicated in this small cohort, although the primary endpoint of safety and tolerability was. The safety profile was consistent with that seen in other studies of EDP1815.

The available evidence to date has found EDP1815 to be well tolerated with evidence for proof of concept as a potential 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 primary study objective is to evaluate the long-term safety and tolerability of EDP1815 in the treatment of atopic dermatitis The primary endpoints to measure this objective will be the incidence and rate per 100 patient-years of treatment-emergent adverse events during the 36-week treatment period and the 4-week follow-up period of this study, and during the treatment period of this study and the relevant parent study.

TEAEs will be defined as all events starting after first dose of study drug and on or before 28 days after last dose for each participant. All TEAEs will be included in the assessments of incidences and rates, regardless of compliance with study medication, use of other medications or deviations from the study protocol.

2.2. Secondary Objectives

The secondary objective of this study is to evaluate the efficacy of long-term treatment with EDP1815 in the treatment of atopic dermatitis

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 other aspects of the efficacy of EDP1815 as a treatment for atopic dermatitis

3. To evaluate the relationship of EDP1815 treatment with biomarkers such as immune protein markers and immune cell RNA profile in blood.

3. STUDY VARIABLES

3.1. Safety Variable(s)

3.1.1. Primary Safety Variable(s)

The primary safety variables will be the incidence and rate per 100 patient-years of TEAEs. Both the period defined by this study alone and the period defined by this study and the relevant parent study will be reported.

Subgroups of TEAEs will be evaluated as follows:

- All TEAEs
- TEAEs of Grade 2 or above
- TEAEs of Grade 3 or above
- Serious TEAEs
- Fatal TEAEs
- TEAEs causing discontinuation of study drug

- Study drug related TEAEs Study (defined by an investigator assessment of possible, probable, or definite relationship to IMP)
- Study drug related TEAEs of Grade 2 or above
- Study drug related TEAEs of Grade 3 or above
- Study drug related serious TEAEs
- Study drug related fatal TEAEs
- Study drug related TEAEs causing discontinuation of study drug

3.1.2. Secondary Efficacy Variable(s)

The following secondary endpoints will be evaluated at all scheduled visits to evaluate the maximum efficacy of EDP1815 in the treatment of atopic dermatitis. For all measures involving changes from baseline, the baseline assessment from the relevant EDP1815 parent study will be used.

- Percentage of participants achieving EASI-50
- 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 IGA of 0 or 1 with a ≥2 point improvement from baseline
- Percentage of participants achieving IGA of 0 or 1
- Percentage of participants achieving IGA of 0

- Mean absolute change and percentage change from baseline in IGA*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% or less

- Mean absolute change and percentage change from baseline in 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

- Mean absolute change from baseline in PP-NRS
- Percentage of participants achieving a reduction of ≥2 in the PP-NRS, of those with a score of ≥2 at baseline
- Percentage of participants achieving a reduction of ≥4 in the PP-NRS, of those with a score of ≥4 at baseline

- Mean absolute change from baseline in SD-NRS
- Percentage of participants achieving a reduction of ≥2 in the SD NRS, of those with a score of ≥2 at baseline

- 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

- Number of courses per patient-year of any rescue medication (not including antibacterial therapy)
- Number of courses per patient-year of topical corticosteroids of any potency
- Number of courses per patient-year of topical tacrolimus (0.1%), topical pimecrolimus (1%) or grade VII topical corticosteroid
- Number of courses per patient year of moderate potency (grade IV and V) topical steroids

3.1.3. 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 (sustained EASI-50 response is defined as one which is present at consecutive visits spanning at least 8 weeks in the absence of rescue medication)

The following endpoints will be used to evaluate other aspects of the efficacy of EDP1815 as a treatment for atopic dermatitis

- Changes from baseline in ADCT scores
- Mean absolute and percentage change in the four body region scores of the EASI
- Percentage of participants achieving at least a 50% reduction in each of the four body region scores of those with a non-zero score for the relevant region at baseline
- Percentage of participants who change response states from Day -1 to Weeks 8, 16, 24 and 36. Response states will be defined using the EASI score percentage change from baseline with categories for ≥25% increase, no change (<25% increase to <25% decrease), 25% to <50% decrease, 50% to <75% decrease, 75% to <90% decrease, ≥90% decrease).
- Daily mean absolute change from baseline in PP-NRS and SD-NRS scores.

The following endpoints will be used to evaluate the relationship of EDP1815 treatment with biomarkers such as immune protein markers and immune cell RNA profile in blood.

- Changes from baseline in serum immune protein markers including IgE
- Changes from baseline in immune cell RNA profile

3.2. Pharmacokinetic and Pharmacodynamic Variable(s)

EDP1815 has no systemic absorption and therefore no systemic exposure. 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.

4. STUDY DESIGN

4.1. Study Description

This is an Open-Label Extension, multicenter study to evaluate the long-term safety, tolerability, and efficacy of EDP1815 in participants with mild, moderate, and severe atopic dermatitis. Participants who have completed the 16-week treatment period in the EDP1815-207 parent study may be eligible to enroll in this study.

4.2. Study Duration per Participant

The total duration of participation in this study is up to a maximum of 40 weeks from Day -1 to follow-up.

Participants will undergo:

- A Day -1 Visit
- A 36-week Treatment Period consisting of 6 study visits
- A 4-week Post-Treatment Follow-up Visit

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. The total number of participants will be dependent on the number of participants who elect and are eligible to participate in the Open Label Extension study following participation in the EDP1815-207 parent study.

4.4. Anticipated Regions and Countries

This study will be conducted at centers located in North America, Europe, and Asia Pacific.

4.5. Schedule of Study Assessments

Table 4-1: Schedule of Assessments

Procedure	Initial Visit (Parent study End of Treatment Visit)	36- Week Treatment Period							End of Study Visit	Early Termination Visit [o]
Day	-1	1	28	56	84	112	168	252	280	
Week	0	1	4	8	12	16	24	36	40	
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+3	
Informed consent [a]	X									
Inclusion and exclusion criteria	X									
Medical history and current medical conditions (including smoking status) [b]	X									
Full Physical examination [c]	X*							X		X
Brief Physical Examination [c]			X	X	X	X	X		X	
Weight [d]	X*		X	X	X	X	X	X	X	X
Height [d]	X									
Pregnancy test [e]	X*		X	X	X	X	X	X	X	X
12-lead ECG [f]	X*		X	X	X	X	X	X	X	X
Laboratory assessments (hematology, biochemistry, urinalysis) [g]	X*		X	X	X	X	X	X	X	X

Procedure	Initial Visit (Parent study End of Treatment Visit)	36- Week Treatment Period							End of Study Visit	Early Termination Visit [o]
Day	-1	1	28	56	84	112	168	252	280	
Week	0	1	4	8	12	16	24	36	40	
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+3	
Biomarker (blood) collection: Inflammation immune surveillance in circulation								X		X
Biomarker (blood) collection: Immune protein markers								X		X
Vital signs [h]	X*		X	X	X	X	X	X	X	X
Participant diary (eDiary) [i]	X		X	X	X	X	X	X	X	X
Randomization (EDP1815-207 Cohort 3) [j]	X									
Dosing [k]		X	→							
IMP Accountability			X	X	X	X	X	X	X	X
vIGA [l]	X*		X	X	X	X	X	X	X	X
BSA involvement (%) [l]	X*		X	X	X	X	X	X	X	X
EASI [l]	X*		X	X	X	X	X	X	X	X
SCORAD [l]	X*		X	X	X	X	X	X	X	X
POEM	X*		X	X	X	X	X	X	X	X
PP-NRS [m]	X*	→								X

Procedure	Initial Visit (Parent study End of Treatment Visit)	36- Week Treatment Period							End of Study Visit	Early Termination Visit [o]
Day	-1	1	28	56	84	112	168	252	280	
Week	0	1	4	8	12	16	24	36	40	
Visit window (days)	--	--	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+3	
SD-NRS [m]	X*	→	→	→	→	→	→	→	→	X
ADCT	X*		X	X	X	X	X	X	X	X
DLQI	X*		X	X	X	X	X	X	X	X
Digital Photographs [n]	X*		X	X	X	X	X	X	X	X
Telephone Call [o]										X
AE SAE Review [p]	X	→	→	→	→	→	→	→	→	X
Concomitant Medication Review	X	→	→	→	→	→	→	→	→	X

*Assessments performed at the End of Treatment Visit of the parent study that do not need to be repeated if this visit occurs on the same day as the Initial Visit of the OLE (Day –1).

[a] Informed consent must be obtained by the Principal Investigator or a Sub-Investigator per Good Clinical Practice (GCP) and local guidelines. The Informed consent form can be provided to the participant prior to the end of treatment visit in the parent study, however, must be signed on Day -1 of this study.

[b] Review any changes to smoking and medical history since baseline of parent study.

[c] A physical examination will be conducted at every visit. At Day -1 and Week 36 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 all other visits, a brief PE will be performed, and the following body systems will be evaluated: general appearance, cardiovascular, respiratory, gastrointestinal, and skin.

[d] BMI will be calculated from the height and weight measurements.

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

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

[g] Results from the laboratory assessments performed at the Day-1 visit will not be required to confirm eligibility for participation in the study. The investigator may use results from the parent study to confirm eligibility.

[h] Blood pressure, heart rate, respiratory rate, and temperature will be measured after the participant has rested for at least 5 minutes in supine position.

[i] Study staff will assist the participant in the transition of studies within their eDiary device at the Day-1 visit. The staff will review the eDiary 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.

[j] EDP1815-207 Cohort 3 participants that are confirmed as eligible to participate in this study at the Day-1 visit will be randomized 1:1 to receive either $1.6x10^{11}$ total cells of EDP1815, or $6.4x10^{11}$ total cells of EDP1815.

[k] Study medication will be dispensed after all Day -1 activities are completed and if the participant is confirmed as eligible to participate in the study. The participant will be instructed to take the first IMP dose on Day 1 at home. The capsules are to be taken once daily at approximately the same time each day. On study visit days, dosing may occur at home prior to the study visit. 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. Participants will be required to record their daily dosing in the eDiary.

[l] 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.

[m] The Pruritus-NRS (worst itch) and the Sleep Disturbance-NRS (SD-NRS) scale will be asked daily from the Day-1 Visit to the Week 40 or Early Termination Visit (if applicable) via the participant eDiary.

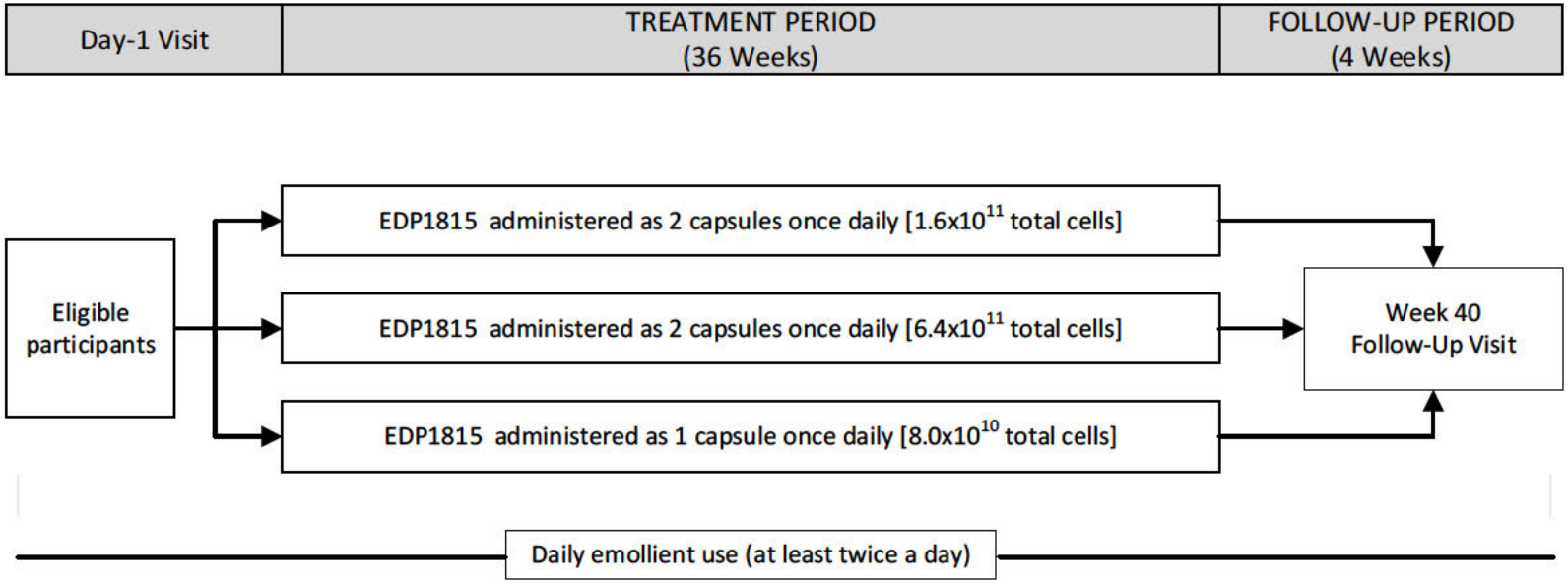
[n] Digital photographs should be taken of the upper and lower body (upper & lower anterior and upper & lower posterior) as half body shots. Additional close-up photographs of up to six specific body areas (i.e., limbs, trunk and back) may also be taken. The same sites photographed in the parent study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

[o] Participants who withdraw from the study early will have an Early Termination Visit. If due to treatment failure, this visit should be arranged within 72 hours of the start of any new 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.

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

4.6. Schematic Study Diagram

Figure 4-1: Schematic Diagram



4.7. Rationale for study design and selection of dose

4.7.1. Dose Rationale

The doses, and corresponding regimen selected for evaluation within this study are:

- Group 1: $1.6x10^{11}$ total cells of EDP1815 administered as 2 capsules once daily.
- Group 2: $6.4x10^{11}$ total cells of EDP1815 administered as 2 capsules once daily.
- Group 3: $8.0x10^{10}$ total cells of EDP1815 administered as 1 capsule once daily.

The doses administered in this study are the same as those administered in the EDP1815-207 parent study.

No placebo will be administered in this study. The following will apply for all EDP1815-207 participants who transition into this study:

- EDP1815-207 Cohort 1 participants will receive $1.6x10^{11}$ total cells of EDP1815 in EDP1815-208 (Group 1)
- EDP1815-207 Cohort 2 participants will receive $6.4x10^{11}$ total cells of EDP1815 in EDP1815-208 (Group 2)
- EDP1815-207 Cohort 3 participants will be randomized 1:1 to receive either $1.6x10^{11}$ total cells of EDP1815 (Group 1), or $6.4x10^{11}$ total cells of EDP1815 (Group 2) in EDP1815-208
- EDP1815-207 Cohort 4 participants will receive $8.0x10^{10}$ total cells of EDP1815 in EDP1815-208 (Group 3)

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.

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 10 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 and vIGA*BSA endpoints, together with improvements in other measures such as the SCORAD. In addition, 7 out of 16 (44%) participants dosed with EDP1815 for 8 weeks achieved an EASI-50 by day 70, compared with 0% in the placebo group. An additional cohort investigated a dose of 6.4 x 10^{11} total cells administered daily for 8 weeks. The above efficacy was not clearly replicated in this small cohort, although the primary endpoint of safety and tolerability was. Given a potential difference in clinical effects seen between the two cohorts which were dosed with EDP1815 produced using different manufacturing processes, the

Company is evaluating drug substance produced using both manufacturing processes in the EDP1815-207 Phase 2 Atopic Dermatitis study.

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 $8.0x10^{11}$ 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 both the EDP1815-207 parent study and subsequently this open label extension study represent commercially acceptable dosing regimens in terms of capsule load and frequency for patients. The dose 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.

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. Any participant who signs the informed consent form will be considered enrolled in the study. Study eligibility procedures will begin after participants sign the informed consent.

5.1. Inclusion criteria

To be eligible to participate in this study, all 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. Must have completed the treatment period in a parent study of EDP1815 in the treatment of atopic dermatitis and complied with the protocol to the satisfaction of the investigator

3. All participants must agree to continue the use of a bland additive-free, sodium lauryl sulfate (SLS)-free, and fragrance-free emollient cream, gel, or ointment at least twice daily (or more, as needed) throughout the study.

4. Continue to meet the following contraception criteria:
    i. Male participants:
        i. A male participant must agree to use contraception 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 or
            2. A WOCBP who continues to follow the contraceptive guidance provided in the parent study during participation in this study, including (if applicable) 7 days prior to the first dose, and for at least 1 complete menstrual cycle (≥30 days) after the last dose.

5.2. Exclusion criteria

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

1. Participants who are currently enrolled in another investigational drug study or plans to receive another investigational agent during this study.

2. 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.

3. Treatment with phototherapy, a biologic agent, or a systemic immunosuppressive agent that could affect AD, including systemic corticosteroids, within 7 days prior to Day -1, unless used as a rescue treatment as part of the parent study protocol.

4. Treatment with topical atopic dermatitis therapies, including topical corticosteroids, topical calcineurin inhibitors, topical PDE-4 inhibitors, and topical JAK inhibitors, within 7 days prior to Day -1, unless used as a rescue treatment as part of the EDP1815-207 protocol.

5. Has received live or live-attenuated vaccination within 7 days prior to Day -1 or intends to have such a vaccination during the study. Non-live and non-replicating vaccines are permitted.

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

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

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study due to failure to meet eligibility criteria. There is no screening period within this study; however, if the participant fails to meet the eligibility criteria, they will be defined as a screen failure. A minimal set of screen failure information is required to confirm 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.

5.4. 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 is 14 consecutive days. Participants should have 80% compliance with IMP administration between any two visits after allowing for permitted interruptions.

Early discontinuation of treatment is defined as permanent stopping of IMP before the Week 36 visit. Investigators will strive to confirm 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 14 consecutive days or multiple dose interruptions resulting in <80% compliance with IMP administration between any two visits may result in discontinuation of IMP and early termination of the participant.

Early withdrawal from the study is defined as failing to complete the 36-week treatment and the follow-up visit.

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 for atopic dermatitis, 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 14 consecutive 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.

5.4.2. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail 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, they 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 participants in this study will be dosed with EDP1815, administered orally for 36 weeks in total. 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 Group 3 is thinner (EC2) than the capsule enteric coating for Groups 1 & 2 (EC1):

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

The drug substance used for Group 1 and Group 3 and 3 uses the same manufacturing process. The drug substance for Group 2 was manufactured using an optimized process to yield a higher concentration of microbe per capsule. Drug substance from these two manufacturing processes has been demonstrated to be similar in both DTH mouse and healthy-volunteer human models. All IMP, regardless of manufacturing processes, is identical in appearance. Additional information is detailed in the EDP1815 IB. The drug product is manufactured by [redacted]

6.2. Investigational Medicinal Product(s) to be Administered

The study IMP (EDP1815) will be administered as capsules for 36 weeks in total.

Study IMP is to be taken with water at approximately the same times each day. 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.

No placebo will be administered in this study.

Table 6-1: IMP to be Administered

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

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).

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 batch number and expiry date 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 confirmed 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 reported as per instructions contained in the EDP1815 IMP Handling Manual.

The Investigator (or designee) will instruct the participant to store the IMP at home 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 verify 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. Participants will utilize an electronic diary (eDiary) from Day -1 through to the Week 40 Follow-Up Visit. It is expected that participants will continue to use the eDiary utilized throughout the EDP1815-207 parent study. The eDiary may be either an application (app) that will be downloaded to the participant's mobile smartphone or an eDiary device specifically designated for the purpose of collecting information as described below for participants who do not have a mobile smartphone or do not wish to download an app to their phone.
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 sleep quality 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 40 Follow-Up or Early Termination Visit (if applicable), 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 discuss with the participant 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/partially used 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 14 consecutive days and the participants should have 80% compliance with IMP administration between any two visits after allowing for permitted interruptions. In cases where IMP was interrupted for less than 14 consecutive days, but overall compliance is below 80%, the possibility for discontinuation should be discussed with the Medical Monitor.

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 confirm 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 will also be recorded

in the participant's eCRF. The participant's dosing eDiary 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 study, 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 the ability of the participant to continue in the study, then this should be discussed with the Medical Monitor.
- 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)**.

All participants must use an emollient at least twice daily throughout the study (**Section 6.9.1.1 Background Therapy)**.

6.9.1.1. Background Therapy

All participants must agree to continue with the use of an emollient at least twice daily. 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 the participant. Participants are not allowed to use emollients containing additives (e.g., urea, ceramide, nicotinamide). Participants should continue this background emollient application twice daily until the Week 40 Follow-up Visit. Missed application of emollient will not be considered protocol deviation(s). 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 record their background therapy via the participant eDiary from Day -1 to the Week 40 Follow-Up Visit (**Section 6.6.1 eDiary**).

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 microbial 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**).

Between Day –1 and Week 16, rescue therapy should be as follows:

For non-sensitive body sites:

- Moderate potency (grade IV and V – **Appendix 14.1**) 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

After Week 16, participants may be prescribed topical calcineurin inhibitors and/or topical corticosteroids of any potency for up to 7 days. It is advised that the lowest effective potency topical corticosteroid is chosen.

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), mupirocin and/or bacitracin, 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

Use of any of the following concomitant medications during the study require the IMP to be immediately discontinued where possible. If a participant requires treatment for atopic dermatitis with a prohibited concomitant medication during the study, they will be classified as a treatment failure. :

- Topical Corticosteroids or Topical Calcineurin Inhibitors (unless used as Rescue Therapy, **Section 6.9.1.2 Rescue Therapy**)
- Topical PDE-4 Inhibitors
- Topical JAK Inhibitors
- Bleach baths
- Phototherapy treatment
- Tanning beds

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

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. The non-intranasal seasonal flu vaccine is permitted, as is the recombinant zoster vaccine (non-live). However, the first dose of IMP should not be taken within a 7-day window of administration of the non-live vaccine or non-replicating 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).

6.10. Blinding

This is an open-label extension study with all participants taking EDP1815 capsules and as such no blinding is required for the study medication in this study.

Investigators and participants will continue to be blinded to the participants treatment assignment in the EDP1815-207 parent study in order to minimize bias.

7. STUDY PROCEDURES BY VISIT

No study procedures should be performed prior to the signing of the informed consent form (ICF). The ICF will need to be signed prior to any conducting any assessments at the Day -1 visit.

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 confirm that there have not been any adverse reactions.

7.1. Day -1 Visit

The Day -1 visit may occur either the same day as the final treatment visit for the parent study, or within 7 days of completing the treatment period of the parent study. If a participant's Day-1 Visit occurs on the same day as the end of treatment visit of the parent study, then any study assessments performed at the final treatment visit of the parent study do not need to be repeated (**See Table 4-1**).

Each site will sequentially assign a unique identifier to each participant that will be used for the duration of the study.

On the day of 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 (**Section 6.9.1.1 Background Therapy)**.

The following procedures will be performed on the Day -1 Visit:

- Obtain written informed consent from participant
- Assessment of inclusion and exclusion criteria
- Collection of demographics including year of birth, age, gender, race, and ethnicity
- Review of changes in medical history and smoking status from the baseline visit of the parent study
- Full physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature) including height and weight measurements BMI will be calculated using the participant's height and weight.
- 12-lead electrocardiogram (ECG)
- Blood sample collection for safety labs
- Urine sample collection for pregnancy testing for women of childbearing potential (WOCBP), and for urinalysis
- AD rating scales - vIGA, EASI, BSA, and SCORAD
- Patient reported clinical rating scales – POEM, DLQI and ADCT
- PP-NRS and SD-NRS scores in participant diary

- 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
- Review and document concomitant medications and therapies
- Assess and document adverse events (AEs) that occur after participant signs informed consent form (ICF)

The participant will be instructed by the investigator or study staff to continue to use their emollient as per protocol requirements.

Enrollment Procedures

- Enroll the participant in IRT after all Day -1 activities are completed and the participant is still deemed eligible to participate.
- If the participant was in Cohort 3 of the EDP1815-207 parent study and is deemed eligible for this study, they will be randomized 1:1 to receive either $1.6x10^{11}$ total cells of EDP1815, or $6.4x10^{11}$ total cells of EDP1815 in this study. An IRT will be used for assigning eligible participants from this cohort into to a dosing group in EDP1815-208. Sufficient IMP will be dispensed to cover the first 4 weeks of the treatment period. The participant will be instructed to take their first dose of IMP at home on Day 1 of the study.
- Assist the participant in the transitioning of apps into the EDP1815-208-study eDiary on their smartphone device and provide instructions on completion of eDiary

7.2. Treatment Period (Week 4 – Week 36)

These visits will take place approximately every month from Week 4 until Week 16, and approximately every 2-4 months from Week 16 until Week 36. Participants may dose at home on the day of the treatment period visits. Prior to these 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. See **Section 6.9.1.1 Background Therapy**.

The following procedures will be performed at each visit during this period:

- Brief physical examination (excluding Week 36 which will consist of a full physical examination)
- Vital signs including weight measurement
- 12-lead ECG
- Urine sample collection for pregnancy testing (women of childbearing potential only)
- Blood sample collection for safety labs
- Blood sample collection for biomarkers (Week 36/Early Termination only)
- Urine for urinalysis
- Digital photographs of the same lesions/ body area taken at the Day -1 Visit
- AD rating scales - vIGA, EASI (and BSA), and SCORAD
- Patient reported clinical rating scales – POEM, DLQI and ADCT
- Collection and or review PP-NRS and SD-NRS scores in participant diary
- Review and documentation of concomitant medications and therapies including emollient use
- Assessment and documentation of adverse events (AEs)

- Review of participant compliance with IMP administration and use of eDiary
- Collection and reconciliation of returned IMP, i.e., IMP accountability. Participants will be required to return all empty cartons and any remaining IMP at the Week 36 visit
- Dispensation of IMP (Excluding Week 36 i.e., the End of Treatment visit)

7.3. Week 40 Follow Up/ End of Study Visit

This visit will be the last visit in the study and will take place approximately 4 weeks after the last dose of IMP. Prior to this 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:

- Brief physical examination
- Vital signs including weight measurements
- 12-lead ECG
- Urine sample collection for pregnancy testing (women of childbearing potential only)
- Blood sample collection for safety labs
- Urine sample collection for urinalysis
- Digital photographs of the same lesions/body area taken at the Day -1 Visit
- AD rating scales - vIGA, EASI (and BSA), and SCORAD
- Patient reported clinical rating scales – POEM, DLQI and ADCT
- Collection and or review of PP-NRS and SD-NRS scores in participant diary
- Review of and documentation of concomitant medications and therapies including emollient use
- Assessment and documentation of adverse events (AEs)
- Removal of eDiary application from smartphone/ collection of eDiary device

7.4. 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 Early Termination Visit will consist of the same assessments and procedures as the End of Treatment Study Visit at Week 36. Once all assessments are complete, study staff will assist the participant to uninstall the mobile application from their smartphone device. 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.

7.5. 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.

7.6. 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.

7.6.1. 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 14.3**. 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 but no safety or efficacy data have yet been reported from these studies.

7.6.2. 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.

7.6.3. EDP1815-208 and COVID-19 Infection

Self-isolation or a positive COVID-19 test in a well participant may not be a reason in itself to stop dosing since 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.

7.6.4. 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 should 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 participant must try and attend all study visits; however, the Week 16 and Week 36 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.

7.7. 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., the participant is physically unable to perform test) will be reported as protocol deviations.

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 any updates to the existing 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 participants will be trained on how to complete the assessments that are considered patient reported outcomes (PRO). PROs should be completed prior to conducting any assessments with the exception of signing the consent form on Day-1. The same reviewer should conduct the skin assessments for a single participant at each visit wherever possible, and at a minimum for the Day -1, Week 16, and Week 36 assessments.

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.

8.2. Validated Investigator's Global Assessment

The Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) will be used to describe the overall appearance of lesions at a given time-point (Simpson E, 2020 Sep). There is a standardized 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

The Dermatology Life Quality Index (DLQI) is a validated PRO instrument comprised of 10 questions to assess how a participant's skin disease has affected their quality of life over the previous 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 participant'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 the worst itch they have experienced over the previous 24 hours (Phan, 2011). The PP-NRS will be completed daily via a daily questionnaire from the Day-1 Visit to the Week 40 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 the worst sleep they have experienced over the previous 24 hours. The SD-NRS will be completed via a daily questionnaire from the Day-1 Visit to the Week 40 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 amount of active atopic dermatitis using the number of participant's handprints, 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 IGA*BSA as a further marker of disease severity and response to treatment (Suh, 2020).

8.9. 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 participant 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) 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, if there is a causal relationship to the medicinal product. A suspected unexpected serious adverse reaction (SUSAR) is another subset of ADR, which includes all adverse reactions that are suspected to be related to an investigational medicine product and are both serious and unexpected.

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 criterion and, instead, should be evaluated for one 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 one 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 confirm complete safety data collection, all AEs occurring during the study (i.e., after the signing of the Informed Consent form) must be reported in the CRF. AEs reported during the parent study that are ongoing at the end of treatment visit will continue to be followed up during EDP1815-208 until resolution or the participants completes the study, whichever is first.

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 immediately 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

At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have used any new medications, changed concomitant medication regimens (prescription or OTC medications), 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 and considered clinically significant will be documented on the AE page in the CRF.

If the participant 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. CTCAE v5.0 grade (Grade 1 – 5)
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 due to the AE
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 **14.4 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.

9.5. 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] Safety personnel will be automatically notified electronically and will retrieve the form.

If the event meets serious criteria and it is not possible to access the EDC system, the back-up paper SAE Form must be completed in English with as much information that is known at the time and emailed to [redacted]. If email is unavailable the SAE can be reported via the [redacted] SAE hotline, and a copy of the completed paper SAE Form faxed to [redacted] 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 an 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] Clinical Safety by phone or email, within 2 weeks of learning of its occurrence. [redacted] Clinical Safety will send the Exposure in Utero Form to the site for completion within 24 hours. This form should be completed and returned to [redacted] Clinical Safety 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] Clinical Safety.

Please see Appendix 14.2 Contraceptive Guidance and Collection of Pregnancy Information for further information.

9.7. Overdose

Excessive dosing (greater than a total of four ((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 confirmed overdose must be promptly reported to [redacted] Clinical Safety 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] Clinical Safety (**Section 9.5 Reporting Serious Adverse Events**).

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

1. Manage the participant 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 in participants with atopic dermatitis 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 adverse events expected in an overdose; however, 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 to detect as early as possible any safety concern(s) related to the IMP so that Investigators, participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Medical Monitor 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 or more SAE considered definitely or probably 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		

For WOCBP, urine pregnancy testing will be conducted at each study visit.

Additional testing may be ordered if needed, to further assess an adverse event (AE), or if there is any suspicion that a participant 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 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 complete a timely review of 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. 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 100 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 20 mL, and the planned maximum amount of blood collected from each participant over 30 days will not exceed 20 mL.

9.11. Biomarkers

9.11.1. Immune Protein Biomarkers

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 the end of study visit of the parent study and at Week 36/Early Termination Visit of this study.

9.11.2. Transcription Analysis

RNA will be collected from whole blood samples at the end of study visit of the EDP1815-207 parent study and at Week 36/Early Termination Visit of this study 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.

9.12. Other Safety Measurements

9.12.3. 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 Baseline Visit of the parent study only. Weight will be assessed at specified visits (without

shoes and outdoor wear e.g., coats). Body mass index will be calculated from the height and weight. Investigators should pay special attention to clinical signs related to previous serious illness.

9.12.4. 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, lungs, abdomen, musculoskeletal, central nervous system, lymph nodes and skin.

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

9.12.5. 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, QT and QTcF (Fridericia) intervals.

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. Additional photographs of up to six specific body areas, i.e., limbs, trunks, and back, will also be taken. The same locations photographed in the parent study should be followed through this 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 guidelines, and applicable regulatory requirements, and to confirm 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) 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) will provide the Sponsor and [redacted] with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, confirm 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 must 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.
- Patient Reported Outcome Measurements (PROs), including POEM, DLQI and ADCT.
- Clinician Outcome Assessments (COAs) including EASI, BSA, IGA, 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 demonstrates 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 confirm 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 Clinical Data Management System (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 Statistical Analysis Plan (SAP) is approved and signed, and any summary/analysis populations are approved, the database will be locked.

10.3.4. Participant Enrollment Log/Participant Identification Code List

The participant's enrollment will be recorded in the Participant 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. 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.

No inferential statistical testing will be performed. Data will be displayed using summary statistics together with 95% confidence intervals where applicable.

Descriptive statistics will also be used extensively in figures to visualize the data. These include but are not limited to mean (SE) plots against time, waterfall plots for individual changes at a specific time point, vertical bar plots showing percentages of participants meeting a specific criterion, scatter plots to look at correlations between endpoints or timepoints.

Data will be listed in data listings.

Baseline will be defined as the baseline value taken from the parent study. In some cases, change prior to first dose of EDP1815 and change since first dose in this study may also be analyzed.

11.2. Definition of Analysis Sets and Defined Data Point Sets

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

11.2.1. Participant Analysis Sets

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

Full analysis set (FAS): The FAS set will consist of all participants who receive any IMP under this protocol.

Other parent study specific analysis sets may also be used in interim analyses which will be defined by the subset of participants from the FAS who were previously enrolled from the specified parent study or studies.

11.2.2. Defined Data Point Sets

The following data point sets (DPS) are defined:

DPS1: Consists of all observed data collected following first dose of IMP under this protocol until the 28 days after the last dose of IMP.

DPS2: Consists of all observed data collected following first dose of active IMP, either in the parent study protocol or this protocol until 28 days after the last dose of IMP under this protocol.

DPS3: Consists of all observed data collected at a scheduled visit in this protocol.

DPS3a: Is a subset of DPS3 for responder efficacy endpoints only, excluding any data collected within 4 weeks after the use of permitted rescue medications or at any time after the use of prohibited medications for atopic dermatitis.

DPS3b: Is a subset of DPS3 for responder efficacy endpoints only, where data collected within 4 weeks after the use of permitted rescue medications, at any time after the use of prohibited medications for atopic dermatitis, or at scheduled endpoints after withdrawal from treatment due to treatment-failure related reasons (related AEs, lack of efficacy, requirement for alternate psoriasis therapy) will be replaced by 'non-responder' .

DPS4: Consists of all observed data collected at a schedule visit in this study or the parent study for participants who enter this study.

DPS4a: Is a subset of DPS4, excluding any data collected within 4 weeks after the use of permitted rescue medications for atopic dermatitis or at any time after the use of prohibited medications for atopic dermatitis.

DPS4b: Is a subset of DPS4 for responder endpoints only, where data collected within 4 weeks after the use of permitted rescue medications for atopic dermatitis, at any time after the use of prohibited medications for atopic dermatitis, or at scheduled endpoints after withdrawal from treatment due to treatment-failure related reasons (related AEs, lack of efficacy, requirement for alternate psoriasis therapy) will be replaced by 'non-responder'.

The FAS with DPS1 and DPS2 will be used to estimate the primary estimands around adverse events, together with estimands based on efficacy count endpoints looking at use of rescue medications.

The FAS with DPS3b and DPS4b will be used to estimate efficacy responder endpoints. In addition DPS3, DPS3a, DPS4 and DPS4a will be used to estimate supplementary estimands for the key efficacy responder endpoints.

The FAS with DPS3a and DPS4a will be used to estimate efficacy continuous endpoints where data is collected at specific timepoints.

The FAS with DPS3 and DPS4 will be used to estimate safety endpoints where data is collected at specific timepoints.

The parent study-specific populations will be used instead of the FAS for interim analyses based on participants taken from a specific study or studies.

11.3. Estimands and Intercurrent Events

11.3.1. Primary Estimand of the Primary Objective

Population: The FAS will be used for all primary estimands. Note that for interim analyses, a parent study specific analysis set may be used in place of the FAS.

The primary safety variables will be the incidence and rate per 100 patient-years of TEAEs.

Safety data will be reported for two periods: (1) the period beginning with the first dose of active IMP in this study (2) the period beginning with the first dose of active IMP across this study and the parent study.

Subgroups of TEAEs will be evaluated as follows:

- All TEAEs
- TEAEs of Grade 2 or above
- TEAEs of Grade 3 or above
- Serious TEAEs
- Fatal TEAEs
- TEAEs causing discontinuation of study drug
- Study drug related TEAEs Study (defined by an investigator assessment of possible, probable, or definite relationship to IMP)
- Study drug related TEAEs of Grade 2 or above
- Study drug related TEAEs of Grade 3 or above
- Study drug related serious TEAEs
- Study drug related fatal TEAEs
- Study drug related TEAEs causing discontinuation of study drug

Population summary measure of interest: For the endpoints looking only at the period defined by this study only, the incidence and rate per 100 patient-years of each category of TEAEs. For the endpoints looking at the period defined since first dose of active IMP by either in this study and the relevant parent study, the rate per 100 patient-years of each category of TEAEs by treatment group.

Treatment groups: For the endpoints looking only at the period defined by this study only, the data will be summarized by daily EDP1815 dose for this study, giving three treatment groups in total:

- $1.6x10^{11}$ total cells per day of EDP1815 (TCPD-1815)
- $6.4x10^{11}$ TCPD-1815
- $8.0x10^{10}$ TCPD-1815

For the endpoints looking at the period defined since first dose of active IMP either in this study or the relevant parent study, data will be summarized by active daily dose across both studies, giving four treatment groups in total:

- $1.6x10^{11}$ TCPD-1815
- $6.4x10^{11}$ TCPD-1815
- $6.4x10^{11}$ to $1.6x10^{11}$ TCPD-1815
- $8.0x10^{10}$ TCPD-1815

Note that the $6.4x10^{11}$ TCPD-1815 group includes patients from the parent study who received this TCPD under both QD and BD dosing schedules. Pooling these patients together assumes safety for these two schedules is similar. If emerging results from the parent studies violate that assumption, then these subgroups may be analyzed separately.

Strategies for intercurrent events:

- Discontinuation of treatment will use a composite strategy as the 'treatment emergent' includes the discontinuation of treatment as part of the definition
- The use of other medications (including permitted rescue therapies), non-compliance with study drug and any deviations from protocol will use a treatment policy strategy in which all data is used regardless of the intercurrent event

11.3.2. Secondary Efficacy Estimands

Population: The FAS will be used for all secondary estimands. Note that for interim analyses, a parent study specific analysis set may be used in place of the FAS.

Population summary measure of interest:

- For continuous endpoints, the mean at each scheduled visit will be used
- For responder endpoints, the percentage of participants with the relevant response will be used
- For rate endpoints, the number of events per patient-year will be used

Treatment groups: Efficacy data will be summarized by daily dose in this study and the parent study, giving a total of seven treatment groups as follows:

- $1.6x10^{11}$ TCPD-1815 in this study, Placebo in parent study
- $1.6x10^{11}$ TCPD-1815 in this study, $1.6x10^{11}$ TCPD-1815 in parent study
- $1.6x10^{11}$ TCPD-1815 in this study, $6.4x10^{11}$ TCPD-1815 in parent study
- $6.4x10^{11}$ TCPD-1815 in this study, Placebo in parent study
- $6.4x10^{11}$ TCPD-1815 in this study, $6.4x10^{11}$ TCPD-1815 in parent study
- $8.0x10^{10}$ TCPD-1815 in this study, Placebo in parent study
- $8.0x10^{10}$ TCPD-1815 in this study, $8.0x10^{10}$ TCPD-1815 in parent study

Further treatment group combinations may be added if additional parent studies feed into this protocol.

As with the safety estimands, the $6.4x10^{11}$ TCPD-1815 group for the parent study treatment arm includes patients from the parent study who received this TCPD under both QD and BD dosing schedules. Pooling these patients together assumes efficacy for these two schedules is similar. If emerging results from the parent studies violate that assumption, then these subgroups of patients may be analyzed separately.

Strategies for intercurrent events for response endpoints:

- Use of rescue medications within 4 weeks, use at any time of other prohibited medications for atopic dermatitis, and discontinuation of treatment for treatment failure-related reasons (related AEs, lack of efficacy, requirement for alternate psoriasis therapy), will be considered using 3 separate strategies. The composite strategy will be used for all response endpoints and in addition, supplementary estimands using the treatment policy

strategy and the while on treatment strategy will be used for key secondary response endpoints (as indicated in **Table 11-1: Secondary Efficacy Estimands)**

  - Treatment policy: including all data collected regardless of use of rescue medications or other prohibited medications for atopic dermatitis
  - While on treatment: excluding all data collected within 4 weeks after use of rescue medications or at any time after use of other prohibited medications for atopic dermatitis
  - Composite strategy: replacing data all data collected within 4 weeks after use of rescue medications, at any time after use of other prohibited medications for atopic dermatitis, or at scheduled visits after treatment discontinuation for treatment-related reasons. Response endpoints will replace such data with 'non-response'.

- Discontinuation of treatment for reasons not related to treatment-failure: a treatment policy strategy will be followed in that there will be no window for days since discontinuation applied to exclude or change data. However, it should be noted that participants will be withdrawn from the study following discontinuation of treatment and as such it is expected that data collected at the scheduled visits will only include participants who are on treatment (or very recently discontinued) with the exception of those visits specifically scheduled to occur 4 and 12 weeks after last dose.
- Non-compliance with study drug and any deviations from protocol not relating to the use of other treatments for atopic dermatitis will use a treatment policy strategy in which all data is used regardless of the intercurrent event.

Strategies for intercurrent events for continuous endpoints:

- Discontinuation of treatment for any reason: a treatment policy strategy will be followed in that there will be no window for days since discontinuation applied to exclude or change data. However, it should be noted that participants will be withdrawn from the study following discontinuation of treatment and as such it is expected that data collected at the scheduled visits will only include participants who are on treatment (or very recently discontinued) with the exception of those visits specifically scheduled to occur 4 and 12 weeks after last dose.
- Non-compliance with study drug and any deviations from protocol not relating to the use of other treatments for atopic dermatitis will use a treatment policy strategy in which all data is used regardless of the intercurrent event

Strategies for intercurrent events for rate endpoints looking at rescue medication will use the same approach as specified for the primary estimands.

Endpoints: Table 11-1 shows the secondary efficacy endpoints defined for this study. All response and continuous endpoints will be summarized at all scheduled visits in both this study and the relevant parent study. Count endpoints will be reported for two periods: (1) the period beginning with the first dose of active IMP in this study (2) the period beginning with the first dose of active IMP across this study and the parent study.

Table 11-1: Secondary Efficacy Estimands

Data Type	Endpoint
Response	EASI-50, EASI-75, EASI-90 IGA of 0 or 1 with a ≥2-point improvement from baseline [1] IGA of 0 or 1[1] IGA of 0 BSA-50, BSA-75[1] BSA ≤3% SCORAD-50, SCORAD-75[1] Improvement of ≥4 points in DLQI from baseline[2] Improvement of ≥2 points and improvement of ≥4 points in PP-NRS score from baseline[2] Improvement of ≥4 points in SD-NRS score from baseline[2] Improvement of ≥4 points in POEM score from baseline[1,2]
Continuous	Change and percentage change from baseline in EASI score Change and percentage change from baseline in IGA*BSA 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[3] Change from baseline in SD-NRS[3]
Rate	Number of courses per patient-year of any rescue medication Number of courses per patient-year of topical corticosteroids of any potency Number of courses per patient-year of topical tacrolimus (0.1%), topical pimecrolimus (1%) or grade VII topical corticosteroid Number of courses per patient year of moderate potency (grade IV and V) topical steroids

[1] For these key efficacy endpoints, supplementary estimands will be shown using a) treatment policy and b) while on treatment strategies for the intercurrent events of use of rescue medication within 4 weeks, prohibited medications, and/or treatment discontinuation for treatment-failure related reasons in addition to the main secondary estimand which uses the composite strategy for these endpoints.

[2] Only for participants with relevant score ≥2 or ≥4 (as applicable) at baseline.

[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.

11.3.3. Exploratory Estimands

Population: The FAS will be used for all exploratory efficacy estimands. Note that for interim analyses, a parent study specific analysis set may be used in place of the FAS.

Details of the endpoints, population summary measures of interest and intercurrent event strategies can be found in Table 11-2.

Table 11-2: Exploratory Estimand Details

Endpoint	Data Point Set	Population summary measure of interest	Intercurrent Event Strategy
Time to first achievement of EASI-50	DPS3b and DPS4b	Cumulative percentage of participants	Composite: Use of rescue medications within 4 weeks and use at any time of other prohibited medications for atopic dermatitis will be considered as non-response.

Time to first achievement of sustained EASI-50		achieving response at each visit	Treatment policy: All data collected will be used regardless of intercurrent events of treatment discontinuation, treatment compliance or deviations from the protocol.
Change from baseline in ADCT score	DPS3 and DPS4	Mean change from baseline at each scheduled visit	Treatment policy for all possible intercurrent events (all data included as collected at scheduled visits)
Change and percentage change from baseline in the each of the four body-region scores of the EASI	DPS3b and DPS4b	Mean change from baseline at each scheduled visit	Composite: Use of rescue medications within 4 weeks and use at any time of other prohibited medications for atopic dermatitis will be imputed using the last available off-rescue value carried forward. Treatment policy: All data collected will be used regardless of intercurrent events of treatment discontinuation, treatment compliance or deviations from the protocol.
Achievement of 50% reduction in each of the four body region scores of the EASI[1]	DPS3b and DPS4b	Percentage of participants achieving response at each visit	Composite: Use of rescue medications within 4 weeks and use at any time of other prohibited medications for atopic dermatitis will be considered as non-response. Treatment policy: All data collected will be used regardless of intercurrent events of treatment discontinuation, treatment compliance or deviations from the protocol.
Change in response states from Day -1 to Weeks 8, 16, 24 and 36. Response states will be defined using the EASI score percentage change from baseline with categories for: ≥25% increase, no change (<25% increase to <25% decrease), 25% to <50% decrease, 50% to <75% decrease, 75% to <90% decrease, ≥90% decrease	DPS3b	Percentage of participants with each change in response state	Composite: Use of rescue medications within 4 weeks and use at any time of other prohibited medications for atopic dermatitis have response state calculated using the last off-rescue value carried forward. Treatment policy: All data collected will be used regardless of intercurrent events of treatment discontinuation, treatment compliance or deviations from the protocol
Absolute change from baseline in PP-NRS and SD-NRS scores.	DPS1 and DPS2	Mean change from baseline at each study day	Composite: Use of rescue medications within 4 weeks and use at any time of other prohibited medications for atopic dermatitis have response state imputed using the last off-rescue value carried forward. Treatment policy: All data collected will be used regardless of intercurrent events of treatment discontinuation, treatment compliance or deviations from the protocol
Changes from baseline in serum immune protein markers including IgE and	DPS3 and DPS4	Mean change from baseline at each scheduled visit	Treatment policy for all possible intercurrent events (all data included as collected at scheduled visits)

in immune cell RNA profile			

1 Only for participants with a non-zero baseline score in the relevant body region

11.3.4. Safety Estimands

All safety estimands (other than those already defined as primary) will use the FAS. A treatment policy approach will be used for all safety estimands, including all data collected regardless of treatment discontinuation, treatment compliance and use of other medications.

Table 11-3: Safety Estimand Details

Data Point Set	Endpoint	Population Summary Measure of Interest
DPS 1	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
DPS 3	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 and rate per 100-patient years

11.4. Planned Analyses

All analyses will be descriptive in nature and no inferential statistics will be performed. 95% confidence intervals of mean changes and incidences or rates may be displayed where appropriate.

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, and to non-compliance with study treatment (including non-compliant emollient use) 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 as part of the intercurrent event strategy, missing data will not be imputed.

Otherwise, missing data will not be imputed.

11.7. Planned Interim Analysis and Data Monitoring

Interim safety and efficacy analyses may be performed throughout the life cycle of the study as required for ongoing evaluation of the risk benefit profile for EDP1815. These may include either all participants enrolled in the study or use a subset of participants who transitioned to this study from a specific parent study. Interim analyses will also incorporate data collected on the parent atopic dermatitis EDP1815 studies which feed into this study. At a minimum, there will be a parent-

study specific analysis performed after all participants from each parent study have completed this study.

11.8. Determination of Sample Size

The sample size of the study will be determined by the number of participants who enroll from qualifying atopic dermatitis parent studies with EDP1815.

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 confirm 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 filed in the ISF.

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 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. 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

14.2. 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 Day -1 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-estrogen 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 where the absence of sperm has been confirmed

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

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 the table 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 (estrogen 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 verified 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 utilized 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 the Day -1 visit.
- 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.

14.3. 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.

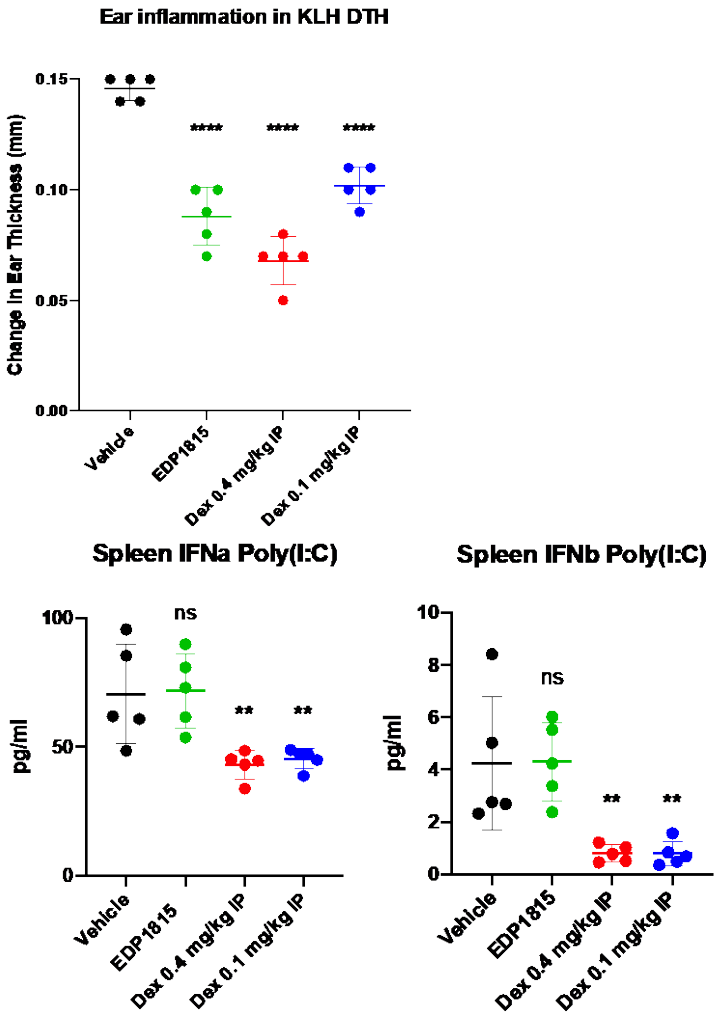
And clinically, treatment with EDP1815 was shown to reduce specific inflammatory myeloid cell cytokines such as IL-6 and IL-8, while not affecting levels of T cell cytokines such as interferon-gamma, produced by circulating peripheral blood mononuclear cells.

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

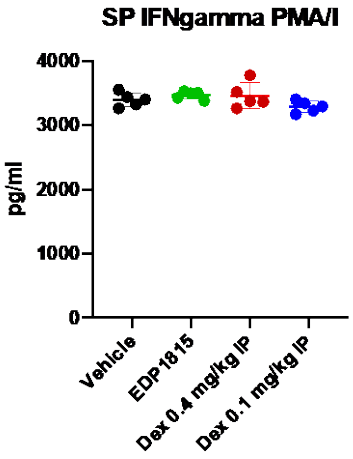
Mice were immunized by subcutaneous injection with KLH emulsified with Complete Freund's Adjuvant. On Day 6 after the sensitization, mice were dosed for 3 days with oral EDP1815, or dexamethasone given intraperitoneally. On day 8, mice were challenged by intradermal ear injection with KLH. The DTH response 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.



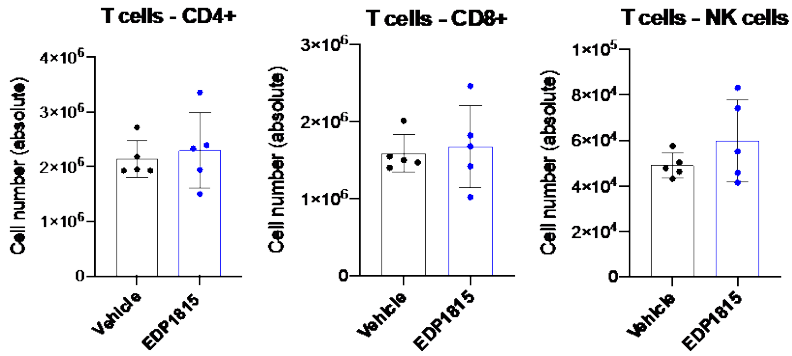
Interferon-gamma production by lymphocytes in vivo

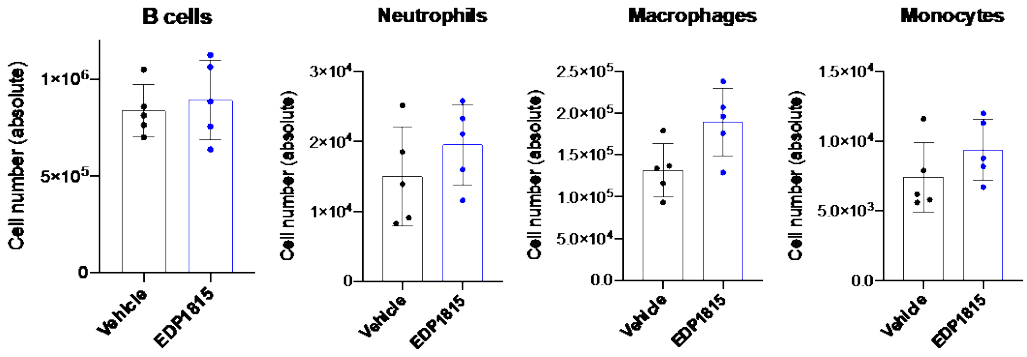
In the same study, spleen cells were restimulated with PMA and ionomycin. PMA activates protein kinase C, while ionomycin is a calcium ionophore, and stimulation with these compounds bypasses the T cell membrane receptor complex and will lead to activation of several intracellular signaling pathways, 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.



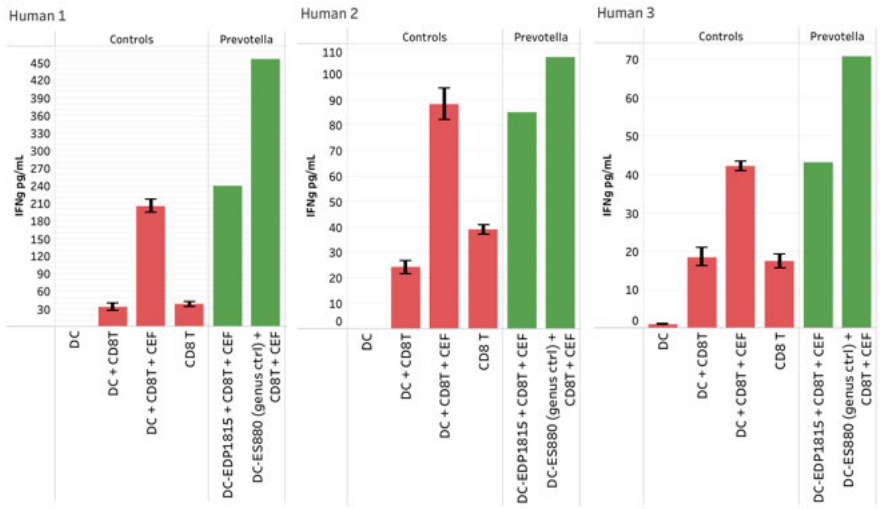


KLH-specific antibody response

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.

14.4. 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]

[redacted]
Date

[redacted]

[redacted]
Date

[redacted]

[redacted]
Date

[redacted]

[redacted]
Date

17.PROTOCOL AMENDMENTS

Document	Protocol Version	Date	Type of Protocol Amendment
Amendment 3	4.0	16 May 2022	Global (Substantial)
Amendment 2	3.0	25 March 2022	Global (Substantial)
Amendment 1	2.0	16 March 2022	Global (Substantial)
Original Protocol	1.0	28 January 2022	Not Applicable

Protocol Amendment 3, Protocol Version 4.0, Dated 16 May 2022

The study protocol has been amended to address comments raised by the FDA following their review of the Protocol Amendment, Protocol Version 3.0, dated 25 March 2022. Additionally, the protocol has been amended to align with the changes made in the EDP1815-207 Parent Protocol to include an additional cohort (Cohort 4). For clarity, the subjects enrolled into this study from the parent study have been grouped according to their dosing regimen. The dose for Cohort 4/ Group 3 is 1 capsule, once daily (0.8×10^{10} 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^{10}, 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.

Major changes are summarized 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
4.6 Schematic Study Design 4.7.1 Dose Rationale 11. Statistics	Updates made to align with the addition of Cohort 4 in the EDP1815-207 parent study; corresponding changes made to the relevant sections as required.	Cohort 4 added to parent protocol EDP1815-207.
6.1 Investigational Medicinal Product(s) Table 6-1: IMP to be Administered	Description of EDP1815 enteric-coated capsules updated to include Cohort 4/Group 3 drug substance description and manufacturing details.	Cohort 4 added to parent protocol EDP1815-207.

4.7.1 Dose Rationale	Additional detail provided on the dose rationale.	Clarification of dose rationale.
9.9 Study Halting Criteria	Halting language amended	Amended per the FDA's recommendation.
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.
11. Statistics	Additional detail added to the definitions of data points sets used in the efficacy estimands, and to the specifications of the treatment groupings used in the summarization of the safety and efficacy estimands.	Amended per the FDA's request for clarification.
14.3 Contraceptive Guidance and Collection of Pregnancy Information	Further clarification provided 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.	Amended to align with parent study.

Protocol Amendment 2, Protocol Version 3.0, Dated 25 March 2022

The study protocol has been amended to address feedback from the FDA on the assessment of AEs.
An additional update was made to include Bilateral tubal ligation as a highly effective contraceptive method.

Section no. and name	Description of change	Brief rationale
9.4.1 Assessments of AEs	AE assessment language updated.	Updated per FDA feedback.
Table 14-1 Highly Effective Contraceptive Methods	Language added to further clarify highly effective methods of contraception.	Table 14-1 amended to include Bilateral tubal ligation as a highly effective contraceptive method.

Protocol Amendment 1, Protocol Version 2.0, Dated 16 March 2022

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 28 January 2022 including to align language on the process of documentation of changes in severity of AEs with the parent study. Additional updates were made to address a change in the Early termination Visit assessment. Major changes are summarized 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 added to clarify how AEs will be solicited from the participant.	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.
9.4.2 Assessments of Severity of AEs	Language added to this section to confirm that Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed.	Alignment with EDP1815-207 parent study protocol.
4.5 Schedule of Study Assessments 7.4 Study Procedures by Visit 9.11. Immune Biomarkers	The schedule of assessments was amended to include a separate column to clarify the assessments to be conducted at the early termination visit. The Early Termination Visit assessments will include end of study biomarker collection.	Amended to include biomarker collection at the Early Termination Visit.