Title: A Phase IIa, Double-Blind, Randomized, Placebo-Controlled, Exploratory Study to Evaluate the Safety, Biological Activity and Pharmacokinetics of GBR 830 in Adult Patients With Moderate-to-Severe Atopic Dermatitis

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CLINICAL STUDY PROTOCOL

Protocol Title	A Phase IIa, Double-Blind, Randomized, Placebo-controlled, Exploratory Study to Evaluate the Safety, Biological Activity and Pharmacokinetics of GBR 830 in Adult Patients With Moderate-to-Severe Atopic Dermatitis
Protocol Number	GBR 830-201
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Phase of Development	IIa
Sponsor	Glenmark Pharmaceuticals SA
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PROTOCOL HISTORY	
Original protocol	Version 1.0, 12-Oct-2015
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Protocol Amendment 3	Version 4.0, 16-Feb-2017

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1. ABBREVIATIONS AND SPECIALIST TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
ANCOVA	Analysis of covariance
AST	Aspartate amino transferase
AUC	Area under the curve
BAS	Biological Activity Set
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CCL	Chemokine ligand
CD	Cluster of differentiation
CFR	Code of Federal Regulations
C_{max}	Maximum observed plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CsA	Cyclosporine A
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cells
dl	Deciliters
DLQI	Dermatology Life Quality Index
DPs	Drug product
DSM	Diagnostic and statistical manual
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase

GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft versus host disease
hARP	Human acidic ribosomal protein
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HV	Healthy volunteers
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IFN	Interferons
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IHC	Immuno-histochemistry
IL	Interleukin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVRS/IWRS	Interactive voice response system / Interactive web response system
KLH	Keyhole limpet hemocyanin
LAR	Legally acceptable representative
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LS	Lesional skin
µl	Microliters
mAb	Monoclonal antibody
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Mins	Minutes
mL	Milliliter
MM	Medical monitor
mM	Millimole

mmHg	Millimeters of mercury
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
MSD	Meso Scale Discovery
msec	Milli second
NA	Not applicable
NaCl	Sodium chloride
NK	Natural Killer
NL	Non-lesional skin
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
OX40L	OX40 ligand
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PI	Principal investigator
PK	Pharmacokinetics(s)
PKAS	Pharmacokinetic analysis set
QTc	Corrected QT
RA	Rheumatoid arthritis
RO	Receptor occupancy
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCORAD	Scoring of Atopic Dermatitis
SOP	Standard operating procedure
sOX40	Serum soluble OX40
sOX40L	Serum soluble OX40 ligand
$t_{1/2}$	Elimination half-life
TARC	Thymus and activation-regulated chemokine (CCL17)
TCS	Topical corticosteroids
TEAEs	Treatment-emergent adverse events
TEWL	Transepidermal water loss
Th1	Type 1 helper T cell
Th2	Type 2 helper T cell
t_{max}	Time at which C_{max} is observed
TNF	Tumor necrosis factor
T_{regs}	Regulatory T cells

TSLP	Thymic stromal lymphopoietin
TT	Tetanus Toxoid
ULN	Upper limit of normal
US	United states
VAS	Visual analogue scale
VLDL	Very low-density lipoprotein
WMA	World Medical Association

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Glenmark Pharmaceuticals SA

Protocol Title

A Phase IIa, Double-Blind, Randomized, Placebo-controlled, Exploratory Study to Evaluate the Safety, Biological Activity and Pharmacokinetics of GBR 830 in Adult Patients With Moderate-to-Severe Atopic Dermatitis

Protocol Number

GBR 830-201

Name of Investigational Product/Code

GBR 830

Name of Active Ingredient

GBR 830

Phase of Development

Phase IIa

Study Rationale

Inhibition of OX40 has emerged as a novel molecular target from research on the biology and pathophysiology that underlie the many facets of inflammation. Recent studies have shown that OX40 and OX40L play a role in the optimal production of T cell cytokines and in regulation of the T-helper (Th) 1/2 balance.

Atopic Dermatitis (AD) is a chronic inflammatory disease, considered a polar Th2 disease, and chronic AD lesions have been shown to have a marked increase in Th2 T cells and related cytokines. OX40 mediates signaling by thymic stromal lymphopoietin (TSLP)-activated dentritic cells (DCs) and is highly upregulated in atopic skin. TSLP-activated DCs have been shown to preferentially activate Th2 T-cell responses in autologous and allogeneic cultures in an OX40-dependent manner.

Data published by Fujita et al, 2011 tested the hypothesis that AD-related DCs induce a Th2-biased immune response. Skin biopsy specimens were collected from patients with chronic AD, psoriasis, and healthy volunteers and DC subsets isolated from the lesional skin were analyzed. OX40L expression was explored in these biopsy specimens as a marker of Th2-driving DCs. A large number of OX40L1 cells were found in AD dermis, with minimal expression in psoriatic and normal dermis.

A study to establish the effect of the systemic immune- suppressant, cyclosporin A (CsA), on AD skin pathology was performed by Khattri et al, 2014. Rapid clinical responses were seen within 2 weeks of CsA treatment, associated with strong suppressions of immune and epidermal phenotypes. AD patients after CsA treatment show high inhibition of IL-22, and significant down-regulation of the Th2 axis.

Recently, a rapid improvement of the AD molecular signature was observed in patients after treatment with 4 weeks with Dupilumab, a targeted Th2 antagonist. Dupilumab suppressed mRNA expression of genes related to activation of T cells, DCs, eosinophils, inflammatory pathways, and Th2-inducing chemokines in skin lesions, with increases or insignificant decreases observed with placebo. These data suggest that the blockade of key

drivers of Th2–mediated inflammation could help in the treatment of AD. AD is therefore considered a suitable model disease for an exploratory signal search study for GBR 830.

The objective of this study is to explore effects of GBR 830 on biomarkers in AD to generate preliminary clinical evidence of biological activity to enable conduct of further definitive efficacy studies in this indication. Preliminary safety and pharmacokinetic (PK) data has been generated in a phase I study in healthy volunteers. The results of non-clinical pharmacology and toxicology studies conducted with GBR 830 to date supporting this study are provided in the Investigator's Brochure (IB).

Study Objective(s):

Primary:

- Safety and tolerability of repeated doses of GBR 830 in adult patients with AD
- Effect of repeated doses of GBR 830 on biomarkers of disease activity in adult patients with AD.

Secondary:

- Effect of GBR 830 on clinical efficacy parameters in adult patients with AD.
- Pharmacokinetics (PK) of repeated doses of GBR 830 in adult patients with AD.
- Immunogenicity of GBR 830 in adult patients with AD.

Exploratory :

- Additional exploratory objectives to understand the mechanism of GBR 830 including effect on cellular infiltrates and immune pathways

Study Population

The target study population is adult males and females with chronic moderate-to-severe AD as defined by Eczema Area and Severity Index (EASI) score of ≥ 12; Scoring of Atopic Dermatitis (SCORAD) of ≥ 20; Investigator's Global Assessment (IGA) score of ≥ 3 at baseline and with history of inadequate response to topical therapies.

Study Design

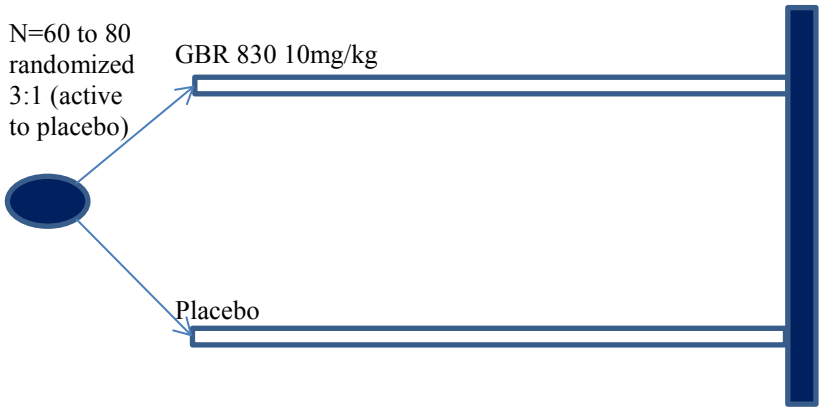
The study is a phase IIa, double-blind, randomized, placebo-controlled, repeated dose study to evaluate safety, biological activity and PK of GBR 830 in adult patients with AD. The study will be conducted in approximately16 centers in US/Canada. The study will be conducted in three phases: screening phase, treatment phase and follow-up phase.

During the screening phase, after providing informed consent, all patients will be screened for eligibility prior to inclusion in the study and sufficient number of patients will be screened to ensure approximately 60 to 80 patients meeting the eligibility criteria will be randomized. At screening, patients will be assessed on EASI, IGA, SCORAD and BSA rating scales for AD. Patients will be withdrawn from use of other medication being used to control their AD as mentioned in prior and concomitant medication section. On Day 1, prior to dosing, patients will be reassessed on EASI, IGA, SCORAD and BSA rating scales for AD to ensure that they qualify for the study.

A sufficient number of patients will be randomized such that approximately 40 evaluable patients complete at least the Day 29 visit. Approximately 60 to 80 patients are planned to be randomized in a ratio of 3:1 to receive GBR 830 (10 mg/kg) or placebo, in a two-arm, parallel design study.

Patients who meet eligibility criteria will undergo Day 1/baseline assessments, randomization, and then receive the first intravenous (IV) infusion of GBR 830 or placebo. Each patient will receive two doses of GBR 830 or placebo administered 4 weeks apart on Day 1 and Day 29. Patients will be closely monitored at the study site for 6 hours after the first infusion (Day 1/baseline) and for 3 hours after the next dose (Day 29). Patients will return for follow-up visits as mentioned in Appendix 1 - schedule of events. The study site will contact patients by telephone approximately 24 hours after each infusion (Days 2 and 30) for concomitant medications and procedures, and a general adverse event (AE) query.

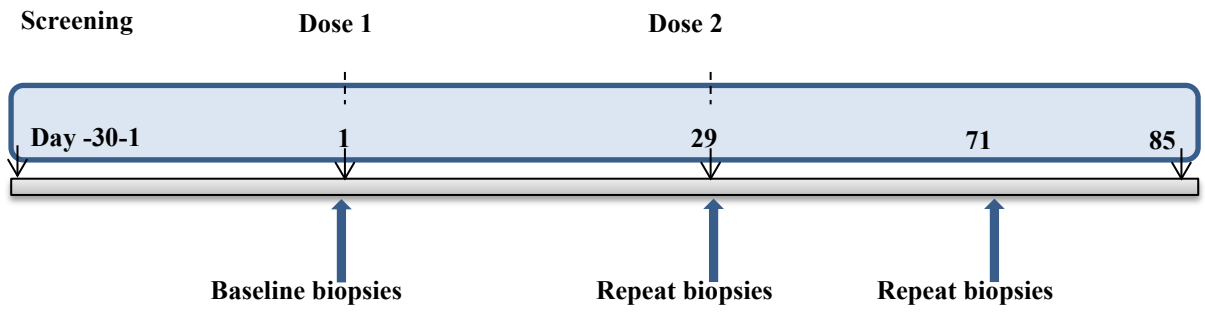
Figure 1: Study design



Apart from the dosing visits, patients will be seen in the clinic on Day 4, 8, 15, 22, 29, 32, 36, 43, 50, 57, 71 and the end of study visit occurs on Day 85 (week 12) for study assessments and PK sample collection.

Skin punch biopsy samples for biomarker analysis will be collected at Day 1/baseline, Day 29 and Day 71. Analyses will be performed where samples are available. A gene/mRNA expression profiling will be performed to evaluate the effects of OX40 blockade on both lesional and non-lesional skin from patients with AD. Changes in gene expression in the AD transcriptome of lesional skin in comparison to a non-lesional molecular phenotype will be used to evaluate treatment-associated effects. In addition any correlation with improvements in disease activity and clinical outcomes will also be evaluated.

Figure 2: Study Flow Chart



Study Endpoint(s)

Primary:

- All Treatment-emergent adverse events (TEAEs) occurring in the study, in terms of nature, onset, duration, severity, relationship and outcome of adverse events (AEs), and serious adverse events (SAEs), in adult patients with moderate-to-severe AD.
- Effect of GBR 830 in adult patients with AD in terms of change from baseline in the active AD mRNA expression signature and the pathologic epidermal phenotype measures obtained from skin biopsies

Secondary:

- Proportion of patients who achieve an IGA score of 0 or 1 at each study visit
- Proportion of patients who achieve an EASI 50 and 75 response at each study visit
- Percent improvement in clinical scores EASI, SCORAD, IGA, BSA (Body surface area), Pruritus Numerical rating scale (NRS) and Dermatology Life Quality Index (DLQI) from baseline to each visit
- Changes from baseline AD activity as determined by changes in trans-epidermal water loss (TEWL)
- PK of GBR 830 in adult patients with moderate to severe AD in terms of: C_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, $t_{1/2}$, volume of distribution, clearance and other parameters assessed as relevant after the first and last doses
- Anti-drug antibodies (ADA) to GBR 830 to evaluate immunogenicity.

Exploratory: Change from baseline in levels of:

- Cytokines and chemokines in serum: IL-22, IL-13, CCL17 (TARC = thymus and activation-regulated chemokine), Eotaxin (CCL11), TSLP, CXCL10 (IP-10), CCL2 (MCP-1), CCL20 (MIP3A),CCL22 (MDC), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL13 (MCP-4), CXCL11 (IP-9; I-TAC), and CXCL9 (MIG)
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells
- Cellular infiltrates (T-cells, dendritic cells) as assessed by CD3, FcEpsilon RI, OX40L, OX40, and MBP.
- Serum total Immunoglobulin E (IgE) serum soluble OX40 (sOX40), serum soluble OX40 ligand (sOX40L), and circulating eosinophil counts

Planned Number of Patients

Approximately 60 to 80 adult patients with AD are planned to be randomized in a ratio of 3 active:1 placebo, to receive either GBR 830 (10 mg/kg) or placebo.

A sufficient number of patients will be randomized such that approximately 40 evaluable patients complete at least the Day 29 visit.

Planned Duration of Patient Participation

Screening phase (4 weeks), study duration (12 weeks), total study duration for each patient (16 weeks).

Inclusion Criteria

Patients eligible for enrolment in the study must meet all of the following criteria:

1. Male or female patients, age ≥ 18 years at the time of informed consent with physician diagnosis of AD for > 1 year; diagnosis of AD as defined by the Hanifin and Rajka criteria for AD.
2. AD involvement of ≥ 10% body surface area (BSA) prior to randomization
3. EASI score of ≥ 12 prior to randomization; SCORAD of ≥ 20 prior to randomization; baseline IGA score of ≥ 3 prior to randomization; and history of inadequate response to a stable (> 1 month) regimen of class 3 or higher strength topical corticosteroids (TCS), or calcineurin inhibitors or for whom topical treatments are otherwise inadvisable (e.g., because of important side effects or safety risks) (Refer to Section 9.1 for details)
4. Patient's body mass index (BMI) should be within the range 18.5–35 kg/m^2 (inclusive); weight must be ≥ 50 kg.
5. Patients deemed fit to receive the study medication, as determined by medical history, vital signs, physical examinations, Electrocardiograms (ECG), laboratory studies, and other tests performed within 30 days prior to drug administration, as judged by the Investigator.
6. Patients must agree to the following requirements during the study:
    a. Women of child-bearing potential and men with partners of child-bearing potential must ensure that two effective means of contraception are used, by them and/or their partners, for the period between signing of informed consent and a minimum of 180 days after the last dose of study drug.

       Acceptable forms of effective contraception include:
       - Established use of oral, injected, or implanted hormonal methods of contraception.
       - Tubal ligation.
       - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
       - Barrier methods only when used consistently with spermicidal foam/gel/film/cream or suppository. Acceptable barrier methods include the following:
           i. Male or female condom.
           ii. Occlusive cap (diaphragm or cervical/vault caps).
       - Male sterilization (with post-vasectomy documentation of the absence of sperm in the ejaculate) (For female patients on the study, the vasectomized male partner should be the sole partner for that patient). If a subject cannot provide written documentation of male sterilization, a verbal statement from the subject will suffice.
       - Maintenance of abstinence when this is in line with the preferred and usual lifestyle of the patient (i.e., not periodic abstinence, such as during ovulation) judged reliable by the Investigator.

       Patients in relation with a same-sex partner do not need to use contraception, if he/she is the sole partner for that patient)

       Of the acceptable forms of effective contraception, at least one method needs to be a barrier method.

b. Male patients should agree not to donate sperm until 180 days after administration of the last dose of the study medication. Female patients should not donate eggs for 180 days following investigational product administration.
c. All female patients must be non-pregnant and non-lactating and test negative for pregnancy at the time of screening and prior to randomization.

7. Female patients of non-child-bearing potential (i.e., are postmenopausal or permanently sterilized [bilateral oophorectomy, hysterectomy, bilateral salpingectomy]). Such patients will not be required to use contraception. Postmenopausal is defined as at least 1 year post cessation of menses (without an alternative medical cause) with follicle stimulating hormone (FSH) ≥ 40.0 mIU/mL.
8. Provide written informed consent
9. Willing and able to comply with all aspects of the protocol including willingness to undergo 4 on study skin biopsies

Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Patients with a history of drug or other allergy considered clinically significant in the opinion of the Investigator, which contraindicates participation or a previous history of hypersensitivity to murine proteins.
2. Patients who have had a live vaccination within 12 weeks before randomization, or intend to have a live vaccination during the course of the study, or have participated in a vaccine clinical trial within 12 weeks prior to randomization
3. History of a serious local infection, systemic infection, or gastrointestinal infection within 12 weeks of baseline; infections requiring systemic antibiotic/ anti-viral/ anti-parasitic/ anti-fungals within 4 weeks of baseline; evidence of clinically significant active infection, or fever ≥38.0^{o}C (100.4^{o}F) within one week of randomization..
4. Patients who have evidence of active or latent tuberculosis as documented medical history, or test positive for QuantiFERON Gold Blood TB Test
5. Patients with evidence of skin conditions at screening that would interfere with evaluations of the study drug
6. Treatment with systemic corticosteroids within 4 weeks before randomization, and topical steroids/tacrolimus and or/pimecrolimus within 1 week before the randomization (except emollients, and mild steroids (class 6 or 7)
7. Treatment with systemic therapy for AD (such as psoralen and ultraviolet A light therapy, cyclosporine, methotrexate, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine), or phototherapy (including ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within the 4 weeks before randomization or other drugs with potential for immunosuppression such as cytotoxic agents or cyclophosphamide taken within 4 weeks prior to randomization.
8. Any cell-depleting agents including but not limited to rituximab: within 6 months prior to the baseline visit, or until lymphocyte and CD 19+ lymphocyte counts return to normal, whichever is longer. Other biologics: within 5 half-lives or 8 weeks prior to the baseline visit, whichever is longer. Allergen immunotherapy within 6 months before the baseline visit.

9. Patients who are immunocompromised, have had a recent (within 3 months before randomization) or current serious systemic or local infection (including infectious mononucleosis-like illness or herpes zoster) suggestive of immunocompromise.
10. Patients who have current or a history of lymphoproliferative disease or history of malignant disease; or signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or active primary or recurrent malignant disease.
11. Patients with history or presence of other inflammatory or auto-immune disease or rheumatological or joint diseases other than AD.
12. History of parasitic infections within 1 year before randomization.
13. History of alcohol or drug abuse or dependence within 2 years of the screening visit.
14. Patients with a positive result from the drug and alcohol screen.
15. Patients who test positive for disease markers of Human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C.
16. Patients with an abnormal ECG (including a QTc >450 msec for men, >460 msec for women) considered clinically significant in the opinion of the Investigator at screening and/or prior to randomization (QTc calculated based on Fridericia's formula).
17. Patients with lab values, which are significantly different from normal reference ranges (as defined in Appendix 2) and/or judged clinically significant by the Investigator, including but not limited to:
    a. Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as determined by the modification of diet in renal disease (MDRD) method.
    b. Alanine amino transferase (ALT) or Aspartate amino transferase (AST) ≥2.5 times upper limit of normal (ULN), and/or serum total bilirubin ≥1.5 times ULN, at screening.
    c. Hemoglobin (Hb) value less than 9 g/dL at screening.
    d. Absolute neutrophil count ≤1,500/µL or absolute lymphocyte count ≤800/µL or platelet count ≤150,000/µL or any abnormal evaluations judged clinically significant by the Investigator at screening and prior to randomization.
18. Patients with any evidence of organ dysfunction or any clinically significant medical history or findings in physical examinations or investigations or has a clinical condition or receiving therapy that, in the opinion of the Investigator, would make the patients unsuitable for study.
19. Patients with a history of current or previous psychiatric illnesses or previous psychiatric events that would either put the patient at undue risk or interfere with study procedures according to the investigator.
20. Treatment with an investigational drug within 8 weeks or within 5 half-lives, if known (whichever is longer), before the baseline visit.

Study-Specific Discontinuation/Withdrawal Criteria

- Withdrawal of consent by the patient to continue in the study.
- Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator.

- At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the patient.
- At the discretion of the Investigator, when he/she believes the patient has not adhered to the study procedures or restrictions.
- A positive pregnancy test.
- Protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study
- A patient requires concomitant medications, which may interfere with the PK of the study drug. Note: withdrawal in such cases will be discussed and mutually agreed by the Investigator and the Sponsor.
- Patients requiring rescue medications or interventions
- The patient for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of AD. In this case, discontinuation from the study should occur prior to introduction of the new agent.
- Disease progression/exacerbation, which in the opinion of the Investigator would require interruption of treatment or premature termination of follow up.
- Patients randomized in the study who withdraw their consent for the first post-baseline skin biopsies.

All efforts will be made to monitor the patients withdrawn during the study for safety and PK analysis, throughout the duration of study.

The decision to discontinue dosing in a patient due to adverse drug effects will be made on the basis of clinical severity and relatedness to study drug. Except in cases of emergency, it is recommended that the Investigator consult the medical monitor (MM) before removing the patient from the study.

Lifestyle and/or Dietary Restrictions

Women of child-bearing potential and men with partners of child-bearing capacity must ensure that two highly effective means of contraception are used, by them and/or their partners, for the period between signing of informed consent and a minimum of 180 days after dosing.

Name of Investigational Product: GBR 830

Dosage Form: Solution for IV infusion.

Dosage: 10 mg/kg

Dosage Frequency: Two doses administered at an interval of once every 4 weeks

Mode of Administration: GBR 830 will be diluted in normal saline and administered as IV infusion over 60 mins.

Placebo/Control/Comparator

Name of Placebo/Control/Comparator: Placebo (formulation buffer)

Dosage Form: Solution for IV infusion

Dosage: NA

Dosage Frequency: Two doses administered at an interval of once every 4 weeks

Mode of Administration: Placebo will be diluted in normal saline and administered as IV infusion over 60 mins.

Duration of Treatment

Two doses of study drug given four weeks apart.

Prohibited Prior and Concomitant Drug/Therapy

Prior Medication:

- Treatment with systemic corticosteroids within 4 weeks before randomization, and topical steroids/ tacrolimus and/or pimecrolimus within 1 week prior to randomization except emollients, and mild steroids (class 6 or 7), applied other than on target area that will be the site for the skin biopsies. Nasal and inhaled corticosteroids use is allowed during study.
- Treatment with systemic therapy for AD (such as psoralen and ultraviolet-A light therapy, cyclosporine, methotrexate, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine), or phototherapy (including ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks before randomization
- Other drugs with potential for immunosuppression such as cytotoxic agents or cyclophosphamide taken within 4 weeks prior to randomization.
- Previous use of biological mAb therapies within 3 months or five half-lives (whichever is longer) of the drug prior to randomization or have previously used biological therapies or allergen immunotherapy for the treatment of AD.
- Complementary or alternate therapies for the treatment of AD/inflammatory conditions. However patients can be included subsequent to an adequate wash-out period (14 days or five half-lives of the complementary or alternate therapy prior to randomization, whichever is longer).

Concomitant Medication:

- All restrictions on the medications listed above in the "prior medication" are applicable for the entire duration of the study

Other concomitant medications that the patient receives on a regular basis may continue if in the opinion of the investigator it does not put the patient at undue risk or nor interfere with the study evaluations. Patients should be stable on allowed concomitant medication for at least 3 months prior to study. All concomitant medications taken by the patient shall also be recorded in the patient diary and Prior & Concomitant Medication Forms of electronic case record form (eCRF).

Assessments

Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic Assessments

Pharmacokinetic Assessments

Blood samples will be obtained at appropriate time points defined in Appendix 1. Concentrations of GBR 830 in serum will be measured at defined time points.

Pharmacokinetic parameters including C_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, $t_{1/2}$, T_{max}, clearance, volume of distribution, and other related PK parameters will be evaluated as relevant.

Biomarker Assessments

Gene expression profiling of AD transcriptome: Skin punch biopsy samples for biomarker analysis will be collected at Day 1/baseline, Day 29 and Day 71. Analyses will be performed where samples are available. Changes in gene expression in the AD transcriptome of lesional skin (LS) in comparison to a non-lesional (NL) molecular phenotype will be used to evaluate treatment-associated effects. The improvement in the AD transcriptome of LS will be defined as treatment-associated changes in gene expression toward a NL molecular phenotype. A ‘‘worsening’’ or exacerbation will be defined as gene expression changes further distinguishing LSs from NLs.

In addition, skin biopsy samples will be evaluated for routine histopathology for evaluation of disease severity.

Leukocyte sub-population cell counts, cytokines, chemokines, TEWL, total IgE, sOX40L, and eosinophil levels will also be measured in the study. Cellular infiltrates (T-cells, dendritic cells) will be assessed by immunohistochemistry of biopsy slides with CD3, FcEpsilon RI, OX40L, OX40, and MBP.

Serum soluble OX40 and OX40L will be measured using PK samples at the time points defined in Appendix 1.

Safety Assessments

Safety and tolerability of GBR 830 including AEs, SAEs, vital signs, laboratory parameters, ECGs, and physical examinations.

Efficacy Assessments

- The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the Investigator or designee on a scale of “0” (absent) through “3” (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, arms, and legs and converted to a score of 0 to 6.
- The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as “A” in the overall SCORAD calculation). The severity of 6 specific symptoms of AD is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as “B” in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as “C” in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C.
- The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe/very severe).
- Pruritus Numerical rating scale (NRS): Patients will record once daily and respond to the following question, “On a scale of 0 – 10, with 0 being “no itch” and 10 being the “worst itch imaginable”, how would you rate your worst degree of itch during the previous 24 hours?” Patient compliance on the pruritus NRS will be followed at each clinic visit.
- Dermatology Life Quality Index (DLQI): The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include “a little,” “a lot,” and “very much” with corresponding scores of 1, 2, and 3 respectively and “not at all”, “not relevant” responses

scored as "0." Totals range from 0 to 30 (less to more impairment) and a 5–point change from baseline is considered clinically relevant.

Immunogenicity:

Blood samples will be obtained at appropriate time points for immunogenicity assessment as defined in Appendix 1. Overall ADA incidence of the study along with patient ADA status and titers for positive confirmed sample will be reported.

Bioanalytical Methods

Validated bio-analytical methods will be used for quantification of serum GBR 830, and for detection and confirmation of anti- GBR 830 antibodies and neutralizing antibodies.

Statistical Methods

Determination of Sample Size

No formal sample size calculation will be performed for this study. The sample size chosen is based on experience from previous studies of similar nature. Patients, who are permanently discontinued from study drug due to reasons other than an AE and before the first post baseline skin biopsies or before receiving two doses of study drug, will not be considered evaluable for the Biological Analysis Set (see Section 13.2). The sample size of 60 to 80 adult patients with AD randomized in ratio of 3:1 (GBR 830 vs placebo), with approximately 40 evaluable patients, is considered to be sufficient to provide descriptive information on the PK, safety, tolerability and potential efficacy of GBR 830.

A patient will be considered evaluable if he/she completes the Day 29 visit and has at least one post-baseline skin biopsy (Visit 7) and received two doses of study drug (Visit 7).

Efficacy Analyses

Analysis of Primary Efficacy Endpoint(s)

Other than safety, the primary endpoint will be absolute change from baseline in the active AD mRNA expression signature. Details of analysis will be specified in the SAP.

Analysis of Secondary Efficacy Endpoint(s)

The statistical methods, including methods for the handling of missing data, for analyzing the secondary endpoints will be fully described in the Statistical Analysis Plan (SAP).

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

PK parameters will be summarized in tabular and graphic form. Results of exploratory analyses will be summarized. Details of PK analysis will be specified in the SAP.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PD parameters will be summarized in tabular and graphic form. Results of exploratory analyses will be summarized.

Details of exploratory analyses to be performed will be specified in the SAP.

Safety Analyses

Adverse events will be summarized by system organ class, preferred term and treatment group. Patients will be counted only once for each preferred term, system organ class, and by the highest severity of an event. Vitals, physical examinations and ECG evaluations will be summarized with descriptive statistics. Laboratory evaluations will be summarized with descriptive statistics at each visit, and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized based on the number and percentage of patients above or below a pre-specified threshold for each test. Details will be presented in the SAP.

Interim Analyses

No interim analysis is planned.

3. INVESTIGATOR'S SIGNATURE

- I have reviewed the clinical protocol.
- I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.
- I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a patient in order to obtain their consent to participate.
- I agree to conduct this study according to this protocol and to comply with its requirements, patient to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.
- I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.
- I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

_____ _____

Name of Investigator, degree: Date

Title:

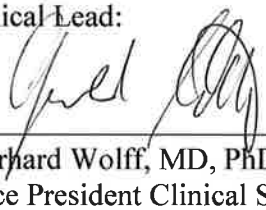
Address and contact details:

4. SPONSOR'S SIGNATURE

This protocol reflects the Sponsor's current knowledge of GBR 830 as applicable to this study. It has been designed to achieve the stated objectives whilst minimizing exposure to, and risk from, both the products being used and the assessments. The assessments are all considered to be appropriate, capable of validating the stated objectives of the study, and of providing the necessary information to ensure patient safety. The protocol has been designed according to the principles of the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and the World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the case report forms.

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures (SOP) required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.
- Signed on behalf of the Sponsor, Glenmark Pharmaceuticals, SA:

Clinical Lead:



02/16/2017

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02/16/17

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Date:

5. BACKGROUND INFORMATION

5.1. Introduction

Allergy and autoimmune diseases affect more than 5-10% of the human population (Cooper et al, 2003) and are associated with high morbidity and mortality. They are chronic debilitating diseases that often attack young adults, especially women, and their social and economic impact is enormous. The limitations of currently available therapies are the slow onset of action, moderate efficacy that declines after several years of treatment, and side effects, the most common being hepatotoxicity, myelosuppression and/or general immunosuppression.

The introduction of biological therapies in the late nineties opened a new era in the treatment of autoimmunity, and exerted a significant impact on the disease course and the quality of life of patients. There are several biologicals that are either approved or in advanced clinical trials, the vast majority of which are used in the treatment of in rheumatoid arthritis (RA), multiple sclerosis (MS) and/or Crohn's disease (Balague et al, 2009).

AD is one of the most prevalent disorders worldwide that affects 4%-7% of adults and 15-25% of children with a significant impact on quality of life of patients. It is a chronic, relapsing inflammatory skin disease characterized by intense pruritus (e.g., itchiness) and by scaly and dry eczematous lesions and often associated with other atopic disorders, such as allergic rhinitis and asthma.

Despite its increasing prevalence worldwide, and the burden on society, specific therapies for AD are still limited, and most commonly used therapies are not based on current mechanistic understanding of the disease. Approximately 20% of patients with AD have moderate to severe disease and generally require systemic therapy, as outlined in several international and regional treatment guidelines (Sidbury et al, 2014, Ring et al, 2012). Most traditional therapies are intended for clinical improvement and symptomatic relief without targeting the specific pathways that initiate and promote AD.

Recent findings link immune and epidermal barrier defects in AD (Raap et al, 2012; Szegedi et al, 2012), suggesting that disease-driving Th2 cytokines involved in AD, such as IL-4, IL-13 and IL-22 inhibit production of barrier proteins (i.e filaggrin and loricrin) and antimicrobial peptides. Thus, inhibition of specific adaptive immune responses or cytokine pathways would be expected to lead to skin barrier repair. Antagonism of this polarized T-cell pathway has the potential to produce fewer immune antagonism related adverse effects, unlike the multiple adverse effects with broad T-cell suppression.

Although there are multiple systemic agents recommended for the treatment of AD, many of the patients still do not achieve optimal efficacy and these treatments have limited efficacy in moderate to severe disease. Drug-specific major safety concerns are another major limitation (Levin et al, 2014). Thus, there remains a significant unmet patient need for new agents with unique mechanisms that can provide improved and sustained skin clearance, and a safety profile

that allows for chronic use. Biologic agents hold the promise for a more targeted, effective and less toxic approach to systemic therapy.

5.2. Investigational Product: Mechanism of Action

GBR 830 is a highly selective, humanized monoclonal antibody (mAb) of the IgG1 subtype which targets the human OX40 receptor; a member of the tumor necrosis factor receptor (TNF-R) gene family. A common function of TNF-R family members is the regulation of T cell-mediated activation and/or apoptosis. OX40 appears to be an excellent target for autoimmune therapy because the T cells that express OX40 are highly enriched for the cells that react with auto-antigen at the site of inflammation. These molecules strongly regulate conventional cluster of differentiation (CD) 4 and CD8 T cells. More recent data have demonstrated their ability to modulate Natural killer (NK) T cell and NK cell function as well as to mediate cross-talk with professional antigen-presenting cells and diverse cell types such as mast cells, smooth muscle cells, and endothelial cells. Additionally, OX40-OX40L interactions alter the differentiation and activity of regulatory T cells (Croft, 2010).

Blocking the OX40/OX40L pathway has been shown to be protective in several animal models of human disease such as asthma, irritable bowel disease, transplant rejection, autoimmune diabetes, graft versus host disease (GvHD), and experimental autoimmune encephalomyelitis, thus validating OX40 as a highly attractive pathway to antagonize in autoimmune diseases. Unlike conventional immunotherapies, blockade of OX40–OX40L interactions seems to inhibit disease-responsible effector T-cell function specifically, and therefore not cause widespread immunosuppression.

5.3. Preclinical Experience

Functional pharmacology studies have demonstrated that GBR 830 is able to block the interaction between OX40 and OX40L and suppress T cell proliferation and allogeneic reactions, such as mixed lymphocyte reactions, with 50% effective concentrations ranging from 0.1 to 3 µg/mL. These studies have also demonstrated that GBR 830 has antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity potential. Consistent with in vitro data, in vivo pharmacology studies demonstrated that GBR 830 could suppress a xenogeneic reaction in a human-mouse GvHD model at doses as low as 1 mg/kg. Studies using a human psoriatic skin transplant model have demonstrated the potent therapeutic anti-psoriatic activity of GBR 830.

Secondary pharmacodynamics studies were conducted to support the safety of GBR 830 administration in humans. GBR 830 was devoid of agonistic potential and did not induce cytokine release in either human peripheral whole blood from healthy volunteers or human peripheral blood mononuclear cell (PBMC) cultures at high density. Taken together, these studies suggest a low risk of inadvertent cytokine release in humans for GBR 830.

In-vitro vaccine reactivation assays suggest that targeting pathological responses driven by memory T cell reactivation with GBR 830 is relevant and potentially more efficacious than blocking CD28 signals. In-vivo studies, conducted to evaluate the effect of GBR 830 treatment

on a T-dependent antibody response to keyhole limpet hemocyanin (KLH), suggest that targeting OX40 has more profound effects on late and memory responses than primary responses. This feature highlights that an antagonistic OX40 treatment in the clinic may display a safer profile in terms of infection susceptibility compared with broader immunosuppressors.

In vivo efficacy of GBR 830 has been demonstrated in an acute GvHD model (mainly prophylactic) and in a human psoriasis xenograft (therapeutic) model. The efficacy in these studies was observed to be similar to or better than that observed with established drugs (efalizumab, etanercept, temovate, cyclosporin). These data confirm the immunomodulatory capabilities of GBR 830 in T cell mediated autoimmune and inflammatory conditions.

Administration of GBR 830 to cynomolgus monkeys at doses up to 100 mg/kg/week for 6 weeks showed no adverse treatment-related changes in any of the evaluated parameters. The no observed adverse effect level (NOAEL) was 100 mg/kg/week.

5.4. Clinical Experience

A Phase I study, entitled "A Two-Part, Phase I, Randomized, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GBR 830 in Adult Healthy Volunteers (Part 1) and a Randomized, Placebo-controlled, Pharmacodynamic Study to Evaluate the Effects of a Single Dose of GBR 830 on the Vaccination Response in Adult, Healthy Volunteers (Part 2)," was conducted to evaluate the safety, PK and PD of GBR 830 in healthy volunteers (GBR 830-101). All subjects completed the study as planned and safety data from this study suggest that single IV doses of GBR 830 are safe and well tolerated up to 10 mg/kg administered over 1 hour.

In Part 1 of the study, sequential doses of 0.3, 1.0, 3.0, and 10 mg/kg were evaluated in cohorts of 8 subjects each (n=6 GBR 830, n=2 placebo/cohort) to determine the safety and pharmacokinetics of single IV doses of GBR 830 in adult healthy volunteers. Immunogenicity was also determined. To fully characterize the safety and PK profile, subjects were evaluated for adverse events, changes in vital signs, ECGs, physical examinations, clinical laboratory test results (including hematology, biochemistry, urinalysis), cytokine analysis (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12 p70, TNFα, Granulocyte-macrophage colony-stimulating factor (GM-CSF), and Interferon (IFN) γ), and flow cytometry (immunophenotyping), relative to baseline and placebo treatment for 10 weeks post dose.

Part 2 of the study evaluated the effect of a one hour infusion of 10 mg/kg dose of GBR 830 (n=10 GBR 830 and n=10 placebo) on vaccination response (e.g., the T cell dependent primary [naïve] antibody response to neo-antigen KLH and T cell dependent recall/memory antibody response to Tetanus Toxoid [TT] antigen) in 20 healthy volunteers. In addition, safety, PK, and immunogenicity of a single IV dose of GBR 830 were evaluated for up to 10 weeks.

5.4.1. Summary of Safety

In the GBR 830-101 study, 52 healthy male and female subjects were randomized to either GBR 830 (n=34) or placebo (n=18). A total of 51 subjects completed the study per protocol; one subject withdrew consent for personal reasons (not related to AEs).

In Part 1 of the study, 47 treatment-emergent adverse events (TEAEs) were reported by 69% (22) of all the subjects (63% of the placebo subjects and 71% of the GBR 830 subjects) (Table 1). Except for 2 events of tooth abscess of moderate intensity, all other TEAEs were mild. All TEAEs had recovered by the time of the last follow-up visit except for 3 TEAEs of mild intensity, not related to study drug, for which the outcomes were either unknown (myalgia) or still present (pain in extremity, muscle twitching).

Table 1 TEAEs (System Organ Class ≥10% Subjects) Study GBR 830-101 Part 1

System organ class	GBR 830 (n=24)	Placebo (n=8)
Any TEAE	17 (71%)	5 (63%)
General Disorders and Administration Site Conditions	7 (29%)	2 (25%)
Nervous System Disorders	6 (25%)	3 (38%)
Infections and Infestations	3 (13%)	1 (13%)

There was no relationship between dose, including placebo, and frequency of TEAEs. The percentage of placebo subjects reporting TEAEs (63%) was within the range reported by subjects who received GBR 830 (50% to 83%). None of the 47 TEAEs in Part 1 was considered related to study drug.

In Part 2 of the study, 34 TEAEs were reported by 65% (13) of all the subjects (80% placebo subjects and 50% GBR 830 subjects) (Table 2). The majority of these TEAEs were mild; only 5 TEAEs were of moderate intensity (influenza-like illness in one placebo subject and influenza-like illness, postural dizziness, pyrexia, and vomiting [all in one GBR 830 subject each]). All TEAEs were resolved by end of the study except for a cough in one subject (GBR 830) (Table 2).

Table 2 TEAEs (System Organ Class ≥10% Subjects) Study GBR 830-101 Part 2

System organ class	GBR 830 (n=10)	Placebo (n=10)
Any TEAE	5 (50%)	8 (80%)
General Disorders and Administration Site Conditions	2 (20%)	3 (30%)
Gastrointestinal Disorders	3 (30%)	1 (10%)
Nervous System Disorders	3 (30%)	3 (30%)
Infections and Infestations	1 (10%)	1 (10%)
Musculoskeletal and Connective Tissue Disorders	2 (20%)	3 (30%)
Vascular Disorders	2 (20%)	0 (0%)

Two TEAEs (headache and nausea) in Part 2 were considered by the Investigator to be related to placebo.

There were no deaths, SAEs, or withdrawals due to AEs during the study.

There were no clinically significant findings with respect to clinical laboratory, vital signs, ECG, physical examination or cytokines in any of the subjects in Part 1 and Part 2. Details of study are presented in the IB.

5.5. Study Rationale

Inhibition of OX40 has emerged as a novel molecular target from research on the biology and pathophysiology that underlie the many facets of inflammation. Recent studies have shown that OX40 and OX40L play a role in the optimal production of T cell cytokines and in regulation of the T-helper (Th) 1/2 balance.

AD is a chronic inflammatory disease in which skin lesions show a marked increase in Th2 cells, Type 22 (T22) cells, and related cytokines i.e., interleukins-4 (IL-4), -5, -6, -9, -10, -13, and -22 (Guttman-Yassky et al, 2007; Guttman-Yassky et al, 2011; Croft, 2010). The OX40/OX40L interaction has been suggested to play an essential role in the pathogenesis of AD. OX40L is expressed by APCs, endothelial cells and T cells, whereas OX40 is found mainly on activated T cells. The expression of OX40L on dendritic cells (DC) is induced by TSLP and TSLP-activated DCs migrate into lymph nodes where OX40/OX40L interaction triggers the differentiation of inflammatory Th2 cells that produce IL-4, IL-5, IL-13 and TNF-a, but no or only little IL-10. Thymic stromal lymphopoietin (TSLP)-activated dentritic cells (DCs) are highly upregulated in atopic skin. TSLP-activated DCs have been shown to preferentially activate Th2 T-cell responses in autologous and allogeneic cultures in an OX40-dependent manner. The finding that OX40/OX40L interactions are the molecular trigger responsible for the induction and maintenance of TH2 responses by TSLP-activated DCs provides a plausible molecular explanation for initiation and maintenance of allergic diseases. These exciting findings suggest that inhibition of OX40 provides a novel therapeutic approach for the treatments of allergic diseases.

Data published by Fujita et al, 2011 tested the hypothesis that AD-related DCs induce a Th2-biased immune response. Skin biopsy specimens were collected from patients with chronic AD, psoriasis, and healthy volunteers and DC subsets isolated from the lesional skin were analyzed. OX40L expression was explored in these biopsy specimens as a marker of Th2-driving DCs. A large number of OX40L1 cells were found in AD dermis, with minimal expression in psoriatic and normal dermis.

A study to establish the effect of the systemic immune- suppressant, cyclosporin A (CsA), on AD skin pathology was performed by Khattri et al, 2014. Rapid clinical responses were seen within 2 weeks of CsA treatment, associated with strong suppressions of immune and epidermal phenotypes. AD patients after CsA treatment show high inhibition of IL-22, and significant down-regulation of the Th2 axis.

Recently, a rapid improvement of the AD molecular signature was observed in patients after treatment with 4 weeks with Dupilumab, a targeted Th2 antagonist. Dupilumab suppressed mRNA expression of genes related to activation of T cells, DCs, eosinophils, inflammatory pathways, and Th2-inducing chemokines in skin lesions, with increases or insignificant decreases observed with placebo. These data suggest that the blockade of key drivers of Th2–mediated inflammation could help in the treatment of AD. AD is therefore considered a suitable model disease for an exploratory signal search study for GBR 830.

The objective of this study is to explore effects of GBR 830 on biomarkers in AD to generate preliminary clinical evidence of biological activity to enable conduct of further definitive efficacy studies in this indication. Preliminary safety and PK data has been generated in a phase I study in healthy volunteers. The results of non-clinical pharmacology and toxicology studies conducted with GBR 830 to date supporting this study are provided in the IB.

5.6. Benefit-Risk Assessment

GBR 830 is a mAb against OX40 (CD134), a co-stimulatory receptor present on activated T cells responsible for the expansion and maintenance of effector and memory immune responses. Blocking the binding of OX40 to its ligand, OX40L (CD252) reduces the longevity and efficacy of these immune responses. GBR 830 is thus being developed to treat a broad range of autoimmune disorders. Glenmark has recently completed a phase I first in human (FIH) study with GBR 830 in the Netherlands and now intends to submit an Investigational New Drug (IND) application for an exploratory Signal Search Study in patients with moderate to severe AD.

Extensive preclinical functional characterization studies have been conducted with GBR 830 to validate the mechanism of action (Details in the IB). The findings from these studies are in agreement with the expected pharmacological effect of an antagonist anti-OX40 antibody.

Secondary pharmacodynamics studies were conducted to support the safety of GBR 830 administration in humans (Details in the IB). GBR 830 was devoid of agonistic potential and did not induce cytokine release in either human peripheral whole blood from healthy volunteers or human peripheral blood mononuclear cell (PBMC) cultures at high density. These studies suggest a low risk of inadvertent cytokine release in humans for GBR 830.

GBR 830 has been administered to cynomolgus monkeys in a 6 week repeat dose toxicology study (Details in the IB). Administration of GBR 830 at doses up to 100 mg/kg/week for 6 weeks showed no adverse treatment-related changes in any of the parameters. The no observed adverse effect level (NOAEL) was 100 mg/kg/week. Based on these data, GBR 830 was considered to have an acceptable safety profile for the phase I clinical study in healthy adult human volunteers.

A two-part, first-in-human, single ascending dose, phase I study of GBR 830 in healthy volunteers (HVs) recently completed. Review of safety data from both Part 1 and Part 2 of this study suggests that GBR 830 is safe and well tolerated. There were no SAEs and almost all AEs were considered by the investigator to be unrelated to the study drugs. There were no clinically meaningful trends in clinical laboratory evaluations, vital signs, ECGs, or physical examination findings.

The safety profile from the phase I study supports further development of GBR 830.

Urgent Safety Measures

The Sponsor and Investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by Contract research organization (CRO) on behalf of the Sponsor, they shall immediately (no later than three days from the date the measures are taken) give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

6. STUDY OBJECTIVE(S)

6.1. Primary Objective(s)

- Safety and tolerability of repeated doses of GBR 830 in adult patients with AD
- Effect of repeated doses of GBR 830 on biomarkers of disease activity in adult patients with AD.

6.2. Secondary Objective(s)

- Effect of GBR 830 on clinical efficacy parameters in adult patients with AD.
- PK of repeated doses of GBR 830 in adult patients with AD.
- Immunogenicity of GBR 830 in adult patients with AD.

6.3. Exploratory Objective(s)

- Additional exploratory objectives to understand the mechanism of GBR 830 including effect on cellular infiltrates and immune pathways

7. STUDY DESIGN

7.1. Study Type/Design

The study is a phase IIa, double-blind, randomized, placebo-controlled, repeated dose study to evaluate safety, biological activity and PK of GBR 830 in adult patients with AD. The study will be conducted in approximately 16 centers in US/Canada. The study will be conducted in three phases: screening phase, treatment phase and follow-up phase.

During the screening phase, after providing informed consent, all patients will be screened for eligibility prior to inclusion in the study and sufficient number of patients will be screened to ensure approximately 60 to 80 patients meeting the eligibility criteria will be randomized. At screening, patients will be assessed on EASI, IGA, SCORAD and BSA rating scales for AD. Patients will be withdrawn from use of other medication being used to control their AD as mentioned in prior and concomitant medication section. On Day 1, prior to dosing, patients will be reassessed on EASI, IGA, SCORAD and BSA rating scales for AD to ensure that they qualify for the study.

A sufficient number of patients will be randomized such that approximately 40 evaluable patients complete at least the Day 29 visit. Approximately -60 to 80 patients are planned to be randomized in a ratio of 3:1 to receive GBR 830 (10 mg/kg) or placebo, in a two-arm, parallel design study.

Patients who meet eligibility criteria will undergo Day 1/baseline assessments, randomization, and then receive the first IV infusion of GBR 830 or placebo. Each patient will receive two doses of GBR 830 or placebo administered 4 weeks apart on Day 1 and Day 29. Patients will be closely monitored at the study site for 6 hours after the first infusion (Day 1/baseline) and for 3 hours after the next dose (Day 29). Patients will return for follow-up visits as mentioned in Appendix 1 - schedule of events. The study site will contact patients by telephone approximately 24 hours after each infusion (Days 2 and 30) for concomitant medications and procedures, and a general AE query.

Apart from the dosing visits, patients will be seen in the clinic on Day 4, 8, 15, 22, 29, 32, 36, 43, 50, 57, 71 and the end of study visit occurs on Day 85 (week 12) for study assessments and PK sample collection.

Skin punch biopsy samples for biomarker analysis will be collected at Day 1/baseline, Day 29 and Day 71. Analyses will be performed where samples are available. A gene/mRNA expression profiling will be performed to evaluate the effects of OX40 blockade on both lesional and non-lesional skin from patients with AD. Changes in gene expression in the AD transcriptome of lesional skin in comparison to a non-lesional molecular phenotype will be used to evaluate treatment-associated effects. In addition any correlation with improvements in disease activity and clinical outcomes will also be evaluated.

The end of the study will be the date of the last study visit for the last patient in the study.

An overview of the study design is shown in Figure 1.

Figure 1 Study Design Schematic

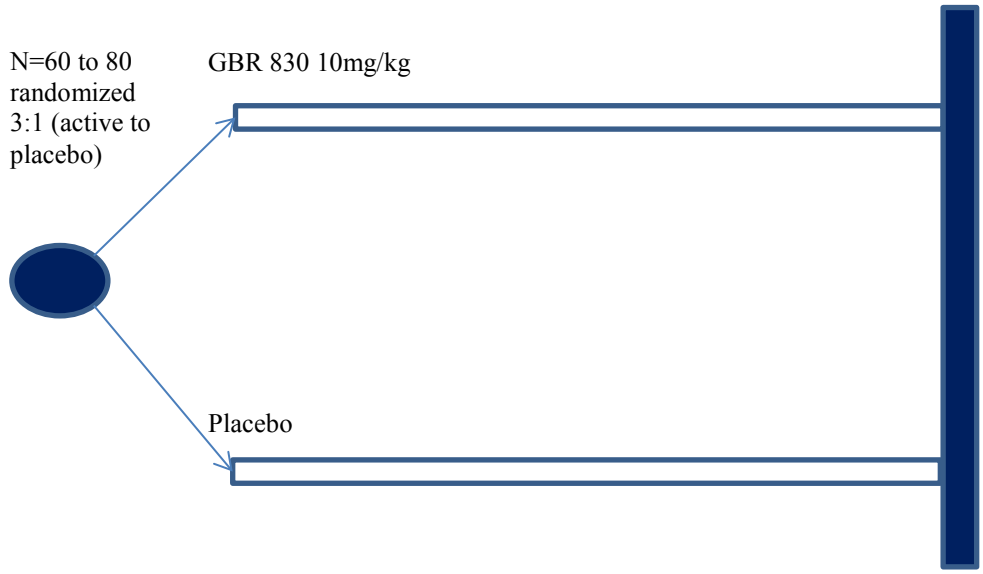
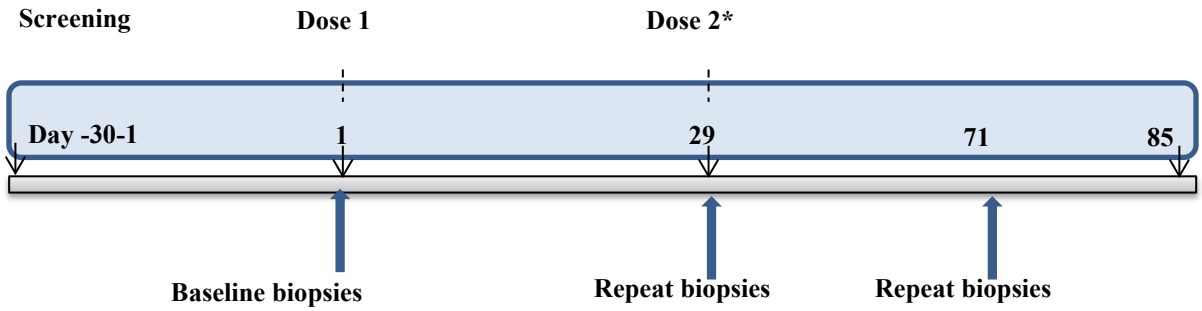


Figure 2 Study Flow Chart



* Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.

7.1.1. Screening Phase

Screening will occur between Day -30 and Day -1. The purpose of the Screening Visit is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each patient and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 15.3.

The study participants must be adult male and female patients with AD.

The Screening Disposition eCRF page must be completed to indicate whether the patient is eligible to participate in the study and to provide reasons for screen failure, if applicable.

At screening, patients will be assessed on EASI, IGA, SCORAD, and BSA for AD. Patients will be withdrawn from use of other medication being used to control their AD as mentioned in prior and concomitant medication section. On Day 1, prior to dosing, patients will be reassessed on EASI, IGA, SCORAD and BSA for AD to ensure that they qualify for the study.

7.1.2. Treatment Phase

The treatment phase consists of the 2 visits (Days 1 and Day 29) which correspond to the study drug dosing days. Study drug IV infusions will be given on these days. Patients will undergo baseline biopsies on Day 1 (pre-dose). All patients will have visit procedures as defined in Appendix 1.

7.1.3. Follow-up

Apart from the dosing visits, patients will be seen in the clinic on Day 4, 8, 15, 22, 29, 32, 36, 43, 50, 57, 71 and the end of study visit occurs on Day 85 (week 12) for study assessments and PK sample collection. Patients will undergo repeat biopsies on Day 29 (pre-dose) and Day 71.

7.1.4. Extension Phase

There is no extension phase planned for this study.

7.2. Discussion of Study Design, Including Choice of Control Groups

The main objective of this phase IIa signal search study is to evaluate the effect of repeated doses of GBR 830 on biomarkers of disease activity in adult patients with moderate to severe AD. The objectives are exploratory in nature to further understand the mechanism of GBR 830 with the help of biomarker data. Recently, improvements of the AD molecular signature were observed in patients after treatment with dupilumab (Hamilton et al, 2014; Beck et al, 2014), a targeted Th2 antagonist, and these changes occurred earlier and were larger than clinical endpoints, suggesting that these are valid endpoints for an exploratory study. Placebo control will provide internal validity for the clinical trial and will improve the sensitivity of the clinical trial for drug related changes and hence suited for an exploratory study.

8. STUDY ENDPOINT(S)

8.1. Primary Endpoint(s)

- All TEAEs occurring in the study, in terms of nature, onset, duration, severity, relationship and outcome of AEs and SAEs, in adult patients with moderate-to-severe AD.
- Effect of GBR 830 in adult patients with AD in terms of change from baseline in the active AD mRNA expression signature and the pathologic epidermal phenotype measures obtained from skin biopsies.

8.2. Secondary Endpoint(s)

- Proportion of patients who achieve an IGA score of 0 or 1 at each study visit
- Proportion of patients who achieve an EASI 50 and 75 response at each study visit
- Percent improvement in clinical scores EASI, SCORAD, IGA, BSA, Pruritus NRS and DLQI from baseline to each visit
- Changes from baseline AD activity as determined by changes in TEWL
- PK of GBR 830 in adult patients with moderate to severe AD in terms of: C_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, $t_{1/2}$, volume of distribution, clearance and other parameters assessed as relevant after the first and last doses
- Anti-drug antibodies to GBR 830 to evaluate immunogenicity.

8.3. Exploratory Endpoint(s)

- Cytokines and chemokines in serum: Interleukin (IL)-22, IL-13, chemokine ligand (CCL)-17 (TARC = thymus and activation-regulated chemokine), Eotaxin (CCL11), TSLP, CXCL10 (IP-10), CCL2 (MCP-1), CCL20 (MIP3A),CCL22 (MDC), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL13 (MCP-4), CXCL11 (IP-9; I-TAC), and CXCL9 (MIG).
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells).
- Cellular infiltrates (T-cells, **d**endritic cells) as assessed by CD3, FcEpsilon RI, OX40L, OX40, and MBP.
- Serum total Immunoglobulin E (IgE), serum soluble OX40 (SOX40), serum soluble OX40 ligand (sOX40L), and circulating eosinophil counts.

8.4. Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD. The safety assessments in this study are standard evaluations to ensure patient safety. The immunogenicity assessment is standard for a monoclonal antibody therapy.

9. PATIENT SELECTION AND WITHDRAWAL CRITERIA

Approximately 60 to 80 patients are planned to be randomized in approximately 16 sites in regions that include US/Canada, such that approximately 40 evaluable patients complete at least the Day 29 visit. Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive investigational products.

Patient eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before patients are included in the study.

Patients, who fail screening on any single criterion, where there is the prospect of their subsequently becoming eligible, may be re-screened on 1 occasion only.

The eligibility of a patient with respect to laboratory criteria will be assessed according to the central laboratory result for the screening sample(s).

9.1. Inclusion Criteria

Patients eligible for enrolment in the study must meet all of the following criteria:

1. Male or female patients, age ≥ 18 years at the time of informed consent with physician diagnosis of AD for > 1 year; diagnosis of AD as defined by the Hanifin and Rajka (Hanifin and Rajka, 1980) criteria for AD.
2. AD involvement of ≥ 10% body surface area prior to randomization.
3. EASI score of ≥ 12 prior to randomization; SCORAD of ≥ 20 prior to randomization; baseline IGA score of ≥ 3 prior to randomization; and history of inadequate response to a stable (> 1 month) regimen of class 3 or higher strength topical corticosteroids (TCS), or calcineurin inhibitors or for whom topical treatments are otherwise inadvisable (e.g., because of important side effects or safety risks)*

   *NOTE: For the purpose of this protocol, inadequate response represents failure to achieve and/or maintain remission or a low disease activity state (e.g., IGA 0=clear to 2=mild) despite treatment with topical corticosteroids of medium to high potency, or topical calcineurin inhibitors as appropriate. Inadequacy of response will be determined based on failure to maintain a low disease activity state despite applications of topical medications on a less intensive maintenance schedule (i.e., 2 days per week). Important side effects or safety risks are those that outweigh the potential treatment benefits (e.g., hypersensitivity reactions, significant skin atrophy, systemic effects, etc., or imminence

thereof), as assessed by the investigator or by patient's treating physician. Medical history provided by physician and/or patient will be used.

4. Patient's body mass index (BMI) should be within the range 18.5–35 kg/m^2 (inclusive); weight must be $\geq$ 50 kg.
5. Patients deemed fit to receive the study medication, as determined by medical history, vital signs, physical examinations, ECG, laboratory studies, and other tests performed within 30 days prior to drug administration, as judged by the Investigator.
6. Patients must agree to the following requirements during the study:
   a. Women of child-bearing potential and men with partners of child-bearing potential must ensure that two effective means of contraception are used, by them and/or their partners, for the period between signing of informed consent and a minimum of 180 days after the last dose of study drug.

      Acceptable forms of effective contraception include:

      i. Established use of oral, injected, or implanted hormonal methods of contraception.
      ii. Tubal ligation
      iii. Placement of an IUD or IUS.
      iv. Barrier methods only when used consistently with spermicidal foam/gel/film/cream or suppository. Acceptable barrier methods include the following:

         (1) Male or female condom.

         (2) Occlusive cap (diaphragm or cervical/vault caps).

      v. Male sterilization (with post-vasectomy documentation of the absence of sperm in the ejaculate) (For female patients on the study, the vasectomized male partner should be the sole partner for that patient). If a subject cannot provide written documentation of male sterilization, a verbal statement from the subject will suffice.
      vi. Maintenance of abstinence when this is in line with the preferred and usual lifestyle of the patient (i.e., not periodic abstinence, such as during ovulation) judged reliable by the Investigator.

      Patients in relation with a same-sex partner do not need to use contraception, if he/she is the sole partner for that patient)

      Of the acceptable forms of effective contraception, at least one method needs to be a barrier method.

   b. Male patients should agree not to donate sperm until 180 days after administration of the last dose of the study medication. Female patients should not donate eggs for 180 days following investigational product administration.

c. All female patients must be non-pregnant and non-lactating and test negative for pregnancy at the time of screening and prior to randomization.

7. Female patients of non-child-bearing potential (i.e., are postmenopausal or permanently sterilized [bilateral oophorectomy, hysterectomy, bilateral salpingectomy]). Such patients will not be required to use contraception. Postmenopausal is defined as at least 1 year post cessation of menses (without an alternative medical cause) with follicle stimulating hormone (FSH) ≥ 40.0 mIU/mL.
8. Provide written informed consent.
9. Willing and able to comply with all aspects of the protocol including willingness to undergo 4 on study skin biopsies.

9.2. Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Patients with a history of drug or other allergy considered clinically significant in the opinion of the Investigator, which contraindicates participation or a previous history of hypersensitivity to murine proteins.
2. Patients who have had a live vaccination within 12 weeks before randomization, or intend to have a live vaccination during the course of the study, or have participated in a vaccine clinical trial within 12 weeks prior to randomization
3. History of a serious local infection, systemic infection, or gastrointestinal infection within 12 weeks of baseline; infections requiring systemic antibiotic/ anti-viral/ anti-parasitic/ anti-fungals within 4 weeks of baseline; evidence of clinically significant active infection, or fever ≥38.0ºC (100.4ºF) within one week prior to randomization.
4. Patients who have evidence of active or latent tuberculosis as documented medical history, or test positive for QuantiFERON Gold Blood TB Test.
5. Patients with evidence of skin conditions at screening that would interfere with evaluations of the study drug.
6. Treatment with systemic corticosteroids within 4 weeks before randomization, and topical steroids/ tacrolimus and or/pimecrolimus within 1 week before the randomization (except emollients, and mild steroids (class 6 or 7).
7. Treatment with systemic therapy for AD (such as psoralen and ultraviolet A light therapy, cyclosporine, methotrexate, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine), or phototherapy (including ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within the 4 weeks before randomization or other drugs with potential for immunosuppression such as cytotoxic agents or cyclophosphamide taken within 4 weeks prior to randomization.

10. Any cell-depleting agents including but not limited to rituximab: within 6 months prior to the baseline visit, or until lymphocyte and CD 19+ lymphocyte count return to normal, whichever is longer. Other biologics: within 5 half-lives or 8 weeks prior to the baseline visit, whichever is longer. Allergen immunotherapy within 6 months before the baseline visit.
11. Patients who are immunocompromised, have had a recent (within 3 months before randomization) or current serious systemic or local infection (including infectious mononucleosis-like illness or herpes zoster) suggestive of immunocompromise.
12. Patients who have current or a history of lymphoproliferative disease or history of malignant disease; or signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or active primary or recurrent malignant disease.
13. Patients with history or presence of other inflammatory or auto-immune disease or rheumatological or joint diseases other than AD.
14. History of parasitic infections within 1 year before randomization
15. History of alcohol or drug abuse or dependence within 2 years of the screening visit.
16. Patients with a positive result from the drug and alcohol screen.
17. Patients who test positive for disease markers of HIV, Hepatitis B or Hepatitis C.
18. Patients with an abnormal ECG (including a QTc >450 msec for men, >460 msec for women) considered clinically significant in the opinion of the Investigator at screening and/or prior to randomization. (QTc calculated based on Fridericia's formula).
19. Patients with lab values, which are significantly different from normal reference ranges (as defined in Appendix 2) and/or judged clinically significant by the Investigator, including but not limited to:
    - Patients with eGFR <60 mL/min/1.73m2 as determined by the MDRD method.
    - ALT or AST ≥2.5 times ULN, and/or serum total bilirubin ≥1.5 times ULN, at screening.
    - Hb value less than 9 g/dL at screening.
    - Absolute neutrophil count ≤1,500/µL or absolute lymphocyte count ≤800/µL or platelet count ≤150,000/µL or any abnormal evaluations judged clinically significant by the Investigator at screening and prior to randomization.
20. Patients with any evidence of organ dysfunction or any clinically significant medical history, or findings in physical examinations or investigations or have a clinical condition or receiving therapy that, in the opinion of the Investigator, would make the patients unsuitable for study.

21. Patients with a history of current or previous psychiatric illnesses or previous psychiatric events that would either put the patient at undue risk or interfere with study procedures according to the investigator.
22. Treatment with an investigational drug within 8 weeks or within 5 half-lives, if known (whichever is longer), before the baseline visit.

9.3. Study Termination, Patient Discontinuation/Withdrawal Criteria

9.3.1. Study Termination Criteria

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate his participation in the study, after consultation with the Sponsor. In addition, the Sponsor may terminate part of, or the entire study, for safety or administrative reasons. A written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and the Regulatory authorities.

9.3.2. Patient Discontinuation/Withdrawal Criteria

A patient may voluntarily discontinue study participation at any time after giving informed consent and before the completion of the follow-up visit (Visit 14 - Day 85). The Investigator may also discontinue the patient's study participation at any time at his/her discretion and for any reason.

The reasons for patient withdrawal will be recorded and may include, but are not limited to:

- Withdrawal of consent by the patient to continue in the study.
- Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator (AE section of eCRF must be completed; includes SAE, death).
- At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the patient.
- At the discretion of the Investigator, when the patient does not adhere to the study procedures or restrictions.
- Protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study.
- A positive pregnancy test.
- A patient requires concomitant medications, which may interfere with the PK of the study drug. Note: withdrawal in such cases will be discussed and mutually agreed by the Investigator and the Sponsor.
- Patients requiring rescue medications or interventions.

- The patient for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of AD. In this case, discontinuation from the study should occur prior to introduction of the new agent.
- Disease progression/exacerbation, which in the opinion of the Investigator would require interruption of treatment or premature termination of follow up.
- Patients randomized in the study who withdraw their consent for the first post-baseline skin biopsies.

The decision to discontinue dosing in a patient due to adverse drug effects will be made on the basis of clinical severity and relatedness to study drug. Except in cases of emergency, it is recommended that the Investigator consult with the Sponsor's medical monitor (MM) before removing the patient from the study.

In case of premature discontinuation, the reason and their cause must be documented. The Investigator (or designee) must document the reason for withdrawal in the End of Study section of the eCRF.

All Follow-up assessments of Visit 14 (Day 85) should be conducted at the Early Withdrawal Visit.

Patients discontinued from the study at any stage will be considered for safety and PK analysis. Patients who are permanently discontinued from study drug due to reasons other than an AE and before the first post baseline skin biopsies or before receiving two doses of study drug, will not be considered evaluable for the Biological Analysis Set (see Section 13.2).

9.3.2.1. Data Collection for Patients Who Permanently Discontinue Study Drug

1. For patients who permanently discontinue study drug and agree to be followed for safety and PK:

   The patient will continue to return for visits as per timing of the visits listed in Appendix 1. For these visits, the safety and PK procedures listed in Section 11.9 should be performed. At the last visit (V14, Day 85) the entire End of Study Assessment should be performed as described in Section 11.8.

23. For patients who permanently discontinue study drug and are not willing to continue in the study:

    The end of study assessments (V14, D85) should be performed at this early withdrawal visit.

9.3.3. Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), drug safety problems, or at the discretion of Glenmark. In addition, Glenmark retains the right to discontinue development of GBR 830 at any time.

If a study is prematurely terminated or discontinued, Glenmark will promptly notify the Investigator. After notification, the Investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time period set by Glenmark. As directed by Glenmark, all study materials must be collected and all CRFs completed to the greatest extent possible.

9.4. Prior and Concomitant Medication(s)

Prohibited Prior Medication:

- Treatment with systemic corticosteroids within 4 weeks before randomization, and topical steroids/ tacrolimus and/or pimecrolimus within 1 week prior to randomization except emollients, and mild steroids (class 6 or 7), applied other than on target area that will be the site for the skin biopsies. Nasal and inhaled corticosteroids use is allowed during study.
- Treatment with systemic therapy for AD (such as psoralen and ultraviolet A light therapy, cyclosporine, methotrexate, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine), or phototherapy (including ultraviolet B or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks before randomization.
- Other drugs with potential for immunosuppression such as cytotoxic agents or cyclophosphamide taken within 4 weeks prior to randomization.
- Any cell-depleting agents including but not limited to rituximab: within 6 months prior to the baseline visit, or until lymphocyte and CD 19+ lymphocyte count return to normal, whichever is longer. Other biologics: within 5 half-lives or 8 weeks prior to the baseline visit, whichever is longer. Allergen immunotherapy within 6 months before the baseline visit.
- Complementary or alternate therapies for the treatment of AD/inflammatory conditions. However patients can be included subsequent to an adequate wash-out period (14 days or five half-lives of the complementary or alternate therapy prior to randomization, whichever is longer).

Prohibited Concomitant Medication:

- All restrictions on the medications listed above in the “prior medication” are applicable for the entire duration of the study.

Other concomitant medications that the patient receives on a regular basis may continue if in the opinion of the investigator it does not put the patient at undue risk or nor interfere with the study evaluations. Patients should be stable on allowed concomitant medication for at least 3 months prior to randomization. Oral contraception must have been taken for a sufficient duration for the medication to be effective according to the product labelling.

- Antihistamines are not allowed on a PRN basis, but they can be taken during the study if the patient has been on a stable dose for 3 months and continues on that stable dose for the entire study duration.
- "Stable" dose would be a daily dose (unless recommended dosing differs from the usual daily regimen) taken 3 months before and continuing throughout the study, to ensure continuity of any effect.
- If the patient has not been on a stable dose for the past 3 months, the subject should either:
  - Have a 4 weeks washout before being randomized into the study
  - Be put on stable dose for 3 months.
- There are miscellaneous medications taken PRN that could be allowed, if they are not expected to have an effect on study parameters, e.g., acetaminophen PRN for headache. Drug with immunosuppressant effects or any prohibited medications are not allowed.
- During the study, if a subject develops allergy symptoms due to allergic rhinitis/allergic conjunctivitis, this subject may use topical nasal sprays/eye drops, but no PRN oral antihistamines will be allowed.

All concomitant medications taken by the patient shall be recorded in the patient diary and Prior & Concomitant Medication Forms of eCRF.

9.4.1. Rescue Medication(s)

In case a patient has a severe flare of disease or severe infection that are deemed by the investigator as necessitating withdrawal from the study and instituting rescue medications, the study medication will be permanently discontinued and the subject will be placed on alternative treatment as soon as possible according to the medical need. These patients will be followed for the whole period of study follow-up (week 12) in order to obtain protocol-specified safety information. Efficacy evaluations will not be performed during this safety follow-up period. If the patient dropped out after Day 29 treatment and biopsies, he will be considered as an evaluable patient for the study.

9.5. Lifestyle and/or Dietary Restrictions

Women of child-bearing potential and men with partners of child-bearing capacity must ensure that two highly effective means of contraception are used, by them and their partners, for the period between signing of informed consent and a minimum of 180 days after dosing.

9.5.1. Contraception

Women of child-bearing potential and men with partners of child-bearing potential must ensure that two highly effective means of contraception are used, by them and/or their partners, for the period between signing of informed consent and a minimum of 180 days after dosing.

Acceptable forms of effective contraception include:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Tubal ligation.
- Placement of an IUD or IUS.
- Barrier methods only when used consistently with spermicidal foam/gel/film/cream or suppository. Acceptable barrier methods include the following:
  - male or female condom
  - occlusive cap (diaphragm or cervical/vault caps)
- Male sterilization (with post-vasectomy documentation of the absence of sperm in the ejaculate) (For female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Maintenance of abstinence when this is in line with the preferred and usual lifestyle of the patient (i.e., not periodic abstinence, such as during ovulation) in a patient judged reliable by the Investigator.

Of the acceptable forms of effective contraception, at least one method needs to be a barrier method.

Notes:

- Female patients not of childbearing potential (i.e. are postmenopausal or permanently sterilized [bilateral oophorectomy, hysterectomy, bilateral salpingectomy]). Such patients will not be required to use contraception.
- Postmenopausal is defined as at least one year post cessation of menses (without an alternative medical cause) with concentrations of FSH $\geq$ 40 mIU/mL.
- Male patients should not donate sperm for 180 days following investigational product administration. Female patients should not donate eggs for 180 days following investigational product administration.

10. TREATMENT OF PATIENTS

10.1. Treatments Administered

- GBR 830 is provided as liquid filled vial formulation available in 10 mL volumes containing GBR 830 at concentrations of 10 mg/mL. GBR 830 solution for infusion will be prepared in normal saline.
- Placebo is provided as liquid filled vial formulation available in 10 mL volumes containing the formulation buffer. Placebo solution for infusion will be prepared in normal saline.
- The GBR 830 dose will be 10 mg/kg.

Administration: investigational product will be administered by continuous slow IV infusion over 60 mins using a commercially available, validated, infusion pump.

10.1.1. Administration

Appropriate aseptic technique should be used while preparing and administering infusions. GBR 830 is provided as liquid filled vial formulation available in 10 mL volumes containing GBR 830 at concentrations of 10 mg/mL.

The investigational product will be diluted with normal saline and administered after normalizing for body weight by continuous slow IV infusion over 60 minutes (+/- 5 mins) using commercially available volumetric or syringe infusion pumps. The infusion is to be performed with the patient in a supine position and/or semi-supine position, with proper documentation noted in the medical records at the site.

The infusion volume must be calculated using the patient's current body weight. In the event of an infusion reaction, for the purposes of patient safety, the rate of infusion may be decreased and the duration extended at the Investigator's discretion. The pharmacist or designee under the direction of the investigator will dispense study drug for each patient according to the protocol and the randomization number assigned through Interactive voice response system / Interactive web response system (IVRS/IWRS). The diluted investigational product should be used within 24 hours and must be stored at 2 to 8°C prior to use. Details of the volume of investigational product required, the concentration to be made, the volume of final infusion to be administered, the infusion sets, and material to be used will be described in a pharmacy manual.

10.1.2. Treatment Compliance

Compliance will be measured by witnessed investigational product administration at the site. Apart from this accountability of vials at the pharmacy, and bio-analytical data will be used to check compliance to the randomization.

Records of treatment compliance for each patient will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

10.1.3. Treatment of Investigational Product Overdose

No data are available with regard to overdose of investigational product in humans. There is no specific antidote to be used in the event of overdose with investigational product. Investigators should use their clinical judgment in treating cases of overdose as dictated by the patient's clinical status.

10.2. Identity of Investigational Product(s)

10.2.1. Chemical Name and Structural Formula of GBR 830

Test drug code:	GBR 830
Generic name:	GBR 830
Chemical name:	GBR 830
Structural formula:	NA

10.2.2. Placebo/Control/Comparator

Placebo will be formulation buffer, diluted in normal saline and administered as IV infusion over 60 mins.

10.2.3. Packaging and Labelling of Investigational Product(s)

GBR 830 drug product (DP) is formulated as a sterile, clear to slightly opalescent, isotonic, colorless to slightly yellowish, aqueous solution containing no preservatives and buffered to a pH of 6.25 for IV administration after dilution in saline. GBR 830 will be supplied in 10-mL single use vials containing 100.0 mg of GBR 830 (nominal 10 mg/mL). In addition, each unit dose vial contains 15mM Histidine, 150 mM NaCl, pH 6.25, and 0.01% Tween 80. The GBR 830 solution for IV infusion will be prepared in normal saline (commercially available normal saline [0.9% sodium chloride]. The placebo for infusion is formulation buffer for IV administration after dilution in saline and will be supplied in 10-mL single use vials. Each unit dose vial contains 15mM Histidine, 150 mM NaCl, pH 6.25, and 0.01% Tween 80. The placebo solution for IV infusion will be prepared in normal saline (commercially available normal saline [0.9% sodium chloride]).

The investigational product vials must be stored refrigerated (2° to 8°C) and protected from light and moisture in a restricted access room at the clinical site. The vials must be allowed to warm to room temperature prior to dispensing.

Glenmark Pharmaceuticals Ltd, or their representative, will provide dosing kits for supply to the sites. The patient-specific dosing kits will be packed and labeled by Glenmark Pharmaceuticals Ltd or their representative in accordance with Good Manufacturing Practice. Sufficient supplies of dosing kits will be provided to the study sites. After study completion, all unused GBR 830 and placebo vials will be destroyed at the clinical site as per the CRO's SOP or returned to the Sponsor, as per written communication from the Sponsor.

The DPs will be labeled in accordance with text that is in full regulatory compliance with each participating country and as necessary translated into the required language(s) for each of those countries.

10.3. Allocation to Treatment Groups

At either a separate consent visit or screening visit, potential study patients will be assigned a screening number. Following confirmation of eligibility, patients will be assigned a randomization number through IVRS/IWRS. The randomization scheme and identification for each patient will be included in the final clinical study report (CSR) for this study. The patient allocation and list of dose/patient numbers are mentioned in Section 10.1.1.

The randomization list will be generated using SAS Version 9.1.3 or higher. All eligible patients entering the study will be randomized to the two treatment arms. If a patient discontinues from the study, the patient number will not be re-used and the patient will not be allowed to re-enter the study.

Patients will be randomly assigned to receive either GBR 830 or placebo in a 3:1 ratio. A randomization number that uniquely identifies each patient and the patient's treatment will be assigned on Day 1. Randomization numbers will be allocated from the schedule in strict chronological order.

A sufficient number of patients (approximately 60 to 80) will be randomized such that approximately 40 evaluable patients complete at least the Day 29 visit.

- For patients randomized prior to protocol version 3 (amendment 2) who do not complete at least the Day 29 visit:
  A replacement patient will be given the patient number corresponding to the person he/she is replacing plus 100. For example, at site 01, if randomized patient 011001 is to be replaced, the subject number for the replacement randomized patient would be 011101. Randomized replacement patient 011101 will receive the same treatment assignment (via IWRS) as the original randomized patient 011001 had received.
- For patients randomized after protocol version 3 (amendment 2 who do not complete at least the Day 29 visit:
  Replacement of patients (to receive the same treatment assignment as the original subject he/she is replacing) will no longer be performed.

Randomization will be done using IVRS/IWRS software.

10.4. Blinding and Unblinding Procedures

The study will be conducted in a double-blind manner. The sponsor will be blinded to the identity of the investigational product and all study data. In the event of a medical emergency when management of a patient's condition requires knowledge of the trial medication, IVRS/IWRS will be used to determine the nature of the trial medication dispensed. If possible, such emergencies should be discussed with the study monitor and the Sponsor prior to disclosure of the treatment allocation. Reasons for breaking a code must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

The following controls will be employed to maintain the double-blind status of the study:

- The placebo will be identical in appearance to the GBR 830 infusion
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure
- Any interim data will be provided in a blinded manner

With the exception of the statistician (who is not a study team member) preparing the randomization and personnel involved in packaging, all clinical and non-clinical staff will remain blinded to the treatment allocation until after the database is locked unless there is a medical event that requires a code break.

10.5. Investigational Product(s) Preparation, Receipt, Storage, Dispensing and Accountability

Investigational product must be stored between 2°C and 8°C. Do not freeze or shake. The investigator (or designee) is responsible for study drug accountability at the site and its documentation. The investigator must also ensure that the dispensing and recording of study drug is performed only by authorized personnel. The study drug records must be readily available for inspection by the study monitor and/or auditor/regulatory agency personnel. No medication (new or used) can be returned to the Sponsor or disposed of at the investigational site until the clinical monitor has verified/reconciled the accuracy of the study drug records at the site and indicated whether the study drug should be destroyed at the site or returned to the Sponsor. The study monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

Clinical staff will dispense the dosing kits at the visits specified in the study protocol. The preparation of the infusion solutions (GBR 830 and placebo) will be performed by a licensed pharmacist or trained designee under the direction of the investigator. The Investigational product will be diluted with a standard 0.9% sodium chloride solution to yield a uniform solution for IV infusion. Foaming or excessive shearing of the protein solution must be avoided. The preparation must be carefully inspected; it should result in a homogeneous-looking clear solution free of visible particles. Direct sunlight should be avoided. The details of preparation and

storage of the infusions are presented in a pharmacy manual. At the time of dispensing, a mandatory verification by a second staff member has to be performed.

11. TIMING OF STUDY PROCEDURES AND ASSESSMENTS

Study procedures and assessments are summarized across all study visits within the Schedule of Events (Appendix 1). The visit windows are mentioned below.

Window for collection of samples for GBR-830 PK analysis:

- V2 and V7:
  - Pre-dose: within 15 minutes before administration of each dose
  - Post-dose:
    - immediately at the end of each infusion± 10 mins;
    - 1.5 hrs ± 10 mins estimated from the start time of infusion
    - 2 hrs ± 10 mins estimated from the start time of infusion
    - 4 hrs ± 10 mins estimated from the start time of infusion
- V3 and V8: 72 hrs ± 24 hrs estimated from the start time of infusion
- V4 and V9: 168 hrs ± 24 hrs estimated from the start time of infusion
- V5 and V10: 336 hrs ± 24 hrs estimated from the start time of infusion
- V6 and V11: 504 hrs ± 48 hrs estimated from the start time of infusion
- V12, V13, V14: 1344 hrs (Day 57) ± 48 hrs, 1680 hours (Day 71) ± 48 hrs, and 2016 hours (Day 85) ± 48 hrs estimated from the start time of first infusion. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.

Window for vital signs:

- V2 and V7:
  - Pre-dose: within 30 minutes before administration of each dose
  - Post-dose:
    - Every half hour during infusion ± 10 mins;
    - 0.5 hrs ± 10 mins estimated from the end time of infusion
    - 1 hr ± 10 mins estimated from the end time of infusion
    - 2 hrs ± 10 mins estimated from the end time of infusion
    - 6 hrs ± 10 mins (In V2 only) estimated from the end time of infusion
    - 3 hrs ± 10 mins (In V7 only) estimated from the end time of infusion
- V3 and V8: 72 hrs± 24 hrs estimated from the start time of infusion
- V4 and V9: 168 hrs ± 24 hrs estimated from the start time of infusion
- V5 and V10: 336 hrs ± 24 hrs estimated from the start time of infusion
- V6 and V11: 504 hrs ± 48 hrs estimated from the start time of infusion

- V12, V13, V14: 1344 hours (Day 57) ± 48 hrs, 1680 hours (Day 71) ± 48 hrs, and 2016 hours (Day 85) ± 48 hrs estimated from the start time of infusion. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.

Window for ECG recording:

- V2:
  - Pre-dose: before administration of each dose
  - Post-dose: 2hrs ± 30 mins and 6hrs ± 30 mins estimated from the end time of infusion
- V3 and V8: 72 hrs± 24 hrs estimated from the start time of infusion
- V4 and V9: 168 hrs ± 24 hrs estimated from the start time of infusion
- V7:
  - Pre-dose: before administration of each dose
  - Post-dose: 2hrs ± 15 mins and 3hrs ± 15 mins estimated from the end time of infusion
- V12, V13, V14: 1344 hours (Day 57) ± 48 hrs, 1680 hours (Day 71) ± 48 hrs, and 2016 hours (Day 85) ± 48 hrs estimated from the start time of first infusion. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.

For all other safety and pharmacodynamics/biomarker/immunogenicity assessments:

- V2: before administration of each dose
- V3 and V8: 72 hrs± 24 hrs estimated from the start time of infusion
- V4 and V9: 168 hrs ± 24 hrs estimated from the start time of infusion
- V5 and V10: 336 hrs ± 24 hrs estimated from the start time of infusion
- V6 and V11: 504 hrs ± 48 hrs estimated from the start time of infusion
- V7: before administration of each dose\
- V12, V13, V14: 1344 hours (Day 57) ± 48 hrs, 1680 hours (Day 71) ± 48 hrs, and 2016 hours (Day 85) ± 48 hrs estimated from the start time of first infusion. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.

In the event that assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK blood sampling will be performed first, followed by ECG and vital signs, with blood sampling exactly on time. Samples collected outside the

window period will be reported as protocol deviations and the actual time point of sampling will be recorded.

11.1. Screening: Visit 1

Patients will go to the site for a screening visit up to 30 days prior to study drug administration Day 1. Informed consent must be obtained at this visit prior to any study procedures are performed. Further details regarding informed consent are provided in Section 15.3.

A screening log will be kept to record patients who sign the informed consent form (ICF) and who are screened. For those patients who are screen failures, a reason for the failure will be documented. Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the study must be explained to the patient and written informed consent must be obtained. Once informed consent has been obtained, the following procedures and evaluations will be performed and recorded.

- A diary, used for the itching scale and other observations required for screening, will be given to each patient when the patient begins the screening period. Patient will be trained on the use of diary. Patient will be instructed to enter the data every morning at a designated time and how to record them. Patient must enter data into the diary every day from start of screening period to end of study visit. Demographic information (Date of birth and/or age, race and ethnicity, gender)
- Height and body weight (measured while wearing indoor clothing and no shoes)
- BMI, calculated as weight (kg)/height $(m)^2$
- Smoking status / intake of tobacco in any other form (including current and historical use of tobacco)
- Alcohol and drug abuse status/ intake in any form
- Medical and surgical history
- Prior and concomitant medications, and AEs
- Detailed physical examination
- Vital signs (pulse, BP-blood pressure, temperature)
- Determine inclusion/exclusion criteria
- 12-lead ECG
- Clinical laboratory tests (collected under fasting conditions; blood sample for hematology, biochemistry tests and urine sample for urinalysis).
- Viral serology (hepatitis B surface antigen [HBsAg], anti- hepatitis B core antigen [Anti-HBc], hepatitis C antibody, human immunodeficiency virus [HIV-1and HIV-2])

- Evidence of active or latent tuberculosis to be documented by medical history or QuantiFERON Gold Blood TB Test. A chest X-ray is not mandatory. QuantiFERON Gold Blood TB Test will be performed in all patients
- Serum Pregnancy test for females (Beta-HCG), serum FSH test for all female patients
- EASI, SCORAD, IGA, BSA measurements

One re-test will be allowed at screening for investigations other than viral serology at the discretion of the investigator in order to confirm findings for clinical conditions that are considered to be acute, reversible, and non-serious.

11.2. Dosing visits (Visits 2 and 7)

The visit 2 will be the baseline visit. Patients will arrive at the study site on the day of dosing (Day 1, Visit 2 and Day 29±1, Visit 7) and will be closely monitored at the study site for 6 hours after the first injection (Day 1/baseline, Visit 2) and for 3 hours after the next dose (Day 29, Visit 7). The following procedures will be conducted and recorded:

- Eligibility criteria and randomization procedures including pre-study restrictions (Visit 2 only)
- Pre-dose drug and alcohol screen
- Body weight and BMI
- Pre-dose brief physical examination of major body systems
- Whole body photography to be taken at Visit 2 (Day 1) only
- Pre- and post-dose vital signs: includes supine or semi-supine measurements BP and pulse; and body temperature. Vitals have to be monitored every half hour during infusion
- Pre- and post-dose 12-lead ECG
- Pre-dose blood samples for routine hematology, biochemistry and urine sample taken for routine urine analysis
- Pre-dose blood samples for serum pregnancy test for females (Beta-HCG) - (Visit 2 only)
- Pre-dose urine pregnancy for females only
- Administration of a single 1-hour IV infusion of IP administered under the supervision of trained study personnel
- Pre-dose EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Blood sample for pre- and post-dose GBR-830 PK analysis
- Pre-dose skin biopsies

- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells), TEWL, total IgE, eosinophil count
- Pre-dose blood samples for immunogenicity, cytokine and exploratory analysis
- Concomitant medications and AEs. The site will contact the subject 24 hours after each infusion by phone

11.3. Follow-up Visits 3 and 8 (Days 4±1 and 32±1)

- Vital signs (pulse, BP, temperature)
- 12-lead ECG
- Clinical laboratory tests (blood sample for hematology, biochemistry and urine sample for urinalysis)
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis

11.4. Follow-up Visits 4 and 9 (Days 8±1 and 36±1)

- Vital signs (pulse, BP, temperature)
- 12-lead ECG
- Clinical laboratory tests (blood sample for hematology, biochemistry; and urine sample for urinalysis)
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells), TEWL, total IgE, eosinophil count
- Whole body photograph to be taken at Visit 4 only

11.5. Follow-up Visits 5 and 10 (Days 15±1 and 43±1)

- Brief physical examination of major body systems
- Vital signs (pulse, BP, temperature)
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs

- Blood sample for GBR-830 PK analysis
- Blood samples for immunogenicity analysis in visit 5 (Day 15)
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells), TEWL, total IgE, eosinophil count
- Whole body photograph to be taken at Visit 10 only

11.6. Follow-up Visits 6 and 11 (Days 22±2 and 50±2)

- Vital signs (pulse, BP, temperature)
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis

11.7. Follow-up Visits 12 and 13 (Days 57±2 and 71±2)

- Vital signs (pulse, BP, temperature)
- 12-lead ECG
- Clinical laboratory tests (blood sample for hematology, biochemistry and urine sample for urinalysis)
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis
- Blood samples for immunogenicity analysis in visit 12 (Day 57)
- Blood samples for cytokine analysis and exploratory analysis on visit 13 (Day 71)
- Skin biopsies on visit 13 (Day 71)
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells), TEWL, total IgE, eosinophil count

11.8. Follow-up Visits (end of study) assessments on Day 85 (±2) include the following:

- Body weight and BMI
- Brief physical examination of major body systems
- Vital signs (pulse, BP, temperature)
- 12-lead ECG

- Clinical laboratory tests (blood sample for hematology, biochemistry and urine sample for urinalysis)
- Blood sample for serum pregnancy tests for all women
- EASI, SCORAD, DLQI, IGA, NRS, BSA measurements
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis
- Blood samples for immunogenicity analysis
- Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells), TEWL, total IgE, eosinophil count
- Whole body photograph

11.9. Early Withdrawal Visit

The Early Withdrawal Visit will be performed as applicable (see Section 9.3.2 for additional information). The end of study assessments will be performed for all patients receiving study drugs who withdraw prematurely from the study. Any patient who is withdrawn must be followed-up as outlined in Section 9.3 and in Appendix 1, but at least for approximately 5 half-lives (56 days) after the last infusion.

In addition, for patients who will be followed for the whole period of study follow-up (week 12) in order to obtain protocol-specified safety information, the following safety and PK parameters will be evaluated according to Appendix 1.

- Brief physical examination of major body systems
- Vital signs (pulse, BP, temperature)
- 12-lead ECG
- Clinical laboratory tests (blood sample for hematology, biochemistry, serum pregnancy tests for all women, and urine sample for urinalysis)
- Concomitant medications and AEs
- Blood sample for GBR-830 PK analysis
- Blood samples for immunogenicity analysis

11.10. Telephone Monitoring

For patients who do not make scheduled study visits or are lost to follow-up a telephone follow up has to be done to evaluate the reason for non-compliance. The study site will contact patients by telephone approximately 24 hours after each infusion of study drug for concomitant

medications and procedures and general AE query. Written documentation must be maintained for all such communications with the patient.

12. STUDY PROCEDURES AND ASSESSMENTS

12.1. Demographic and Other Pretreatment Assessments

12.1.1. Demography

Patient demography information will be collected at the Screening visit. Demographic information includes date of birth (or age), gender, race/ethnicity, height and weight.

12.1.2. Medical History and Physical Examinations at Screening

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. Smoking, alcohol and drug abuse history will also be recorded. All relevant medical and surgical history must be noted in the Medical and Surgical History eCRF form.

Screening Physical examinations will be comprehensive and documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical and Surgical History eCRF form.

12.1.3. QuantiFERON Gold Blood TB Test

A whole blood sample will be collected from each patient at the screening visit for the

QuantiFERON Gold Blood TB Test. Detailed instructions for blood sample collection, preparation, and shipping are provided in the central laboratory manual.

In addition, eligibility criteria will be assessed at baseline prior to randomization.

12.2. Efficacy Assessments

12.2.1. EASI

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, arms, and legs and converted to a score of 0 to 6 (Hanifin et al, 2001).

12.2.2. SCORAD

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology 1993 - SCORAD Index, 1993). The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the

overall SCORAD calculation). The severity of 6 specific symptoms of AD is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C (Kunz et al, 1997).

12.2.3. IGA

The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe/very severe). The proportion of patients who achieve an IGA 0 or 1 score is another key secondary endpoint, which will be included in the primary analysis.

12.2.4. NRS

Pruritus Numerical rating scale (NRS): Patients will record once daily and respond to the following question, "On a scale of 0 – 10, with 0 being no itch and 10 being the worst itch imaginable, how would you rate your worst degree of itch during the previous 24 hours?" Patient compliance on the pruritus NRS will be followed at each clinic visit.

12.2.5. DLQI

Dermatology Life Quality Index (DLQI): The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "a little," "a lot," and "very much" with corresponding scores of 1, 2, and 3 respectively and "not at all", "not relevant" responses scored as "0." Totals range from 0 to 30 (less to more impairment) and a 5–point change from baseline is considered clinically relevant ((Basra et al, 2008; Finlay and Khan, 1994).

12.3. Pharmacokinetic, Pharmacodynamic, Biomarker and Pharmacogenomic Assessments

12.3.1. Pharmacokinetic Assessments

Blood samples will be collected as per routine phlebotomy procedures and at time points specified in the Schedule of Events (Appendix 1). Briefly, blood samples (1 x 3.5 mL each) will be collected during the course of the study through indwelling cannula placed in forearm veins or alternatively, by a fresh clean venipuncture using a disposable sterilized syringe and a needle. The cannulae will be maintained patent as per local practice. Do not use heparin.

The minute of collection of each blood sample will be recorded. In any case actual time points will be used during PK calculations.

The details of sample collection, processing and storage will be outlined in a separate lab manual. The samples will be shipped to the specified bioanalytical lab. Serum concentrations of GBR 830 will be quantified using a validated enzyme-linked immunosorbent assay (ELISA) method.

12.3.2. Immunogenicity Assessments

Blood samples will be collected at appropriate time points defined in Appendix 1, to evaluate anti-drug antibodies to GBR 830, as per procedures similar to collection of PK samples. Antibodies to GBR 830 will be detected and confirmed using a validated ELISA method. The details of sample collection, processing and storage will be outlined in a separate lab manual. The samples will be shipped to the specified bioanalytical lab

12.3.3. Biomarker Assessments

12.3.3.1. Flow cytometry/Leukocyte sub-population cell counts

Blood samples will be collected at appropriate time points defined in Appendix 1. The details of sample collection, processing and storage will be outlined in a separate lab manual.

12.3.3.2. Cytokines and Chemokines

Blood samples will be collected at appropriate time points defined in Appendix 1. The details of sample collection, processing and storage will be outlined in a separate lab manual.

12.3.3.3. Total IgE

Patients with AD often have elevated IgE. Total IgE levels have been found to modestly correlate with AD severity and may be involved in the pathogenesis of the disease. Changes in total IgE reflects not only on AD, but atopy in general. Baseline IgE levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of GBR 830 on total IgE. Detailed instructions for blood sample collection will be outlined in a separate lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.

12.3.3.4. Transepidermal Water Loss

Transepidermal water loss is a skin barrier function test that measures perspiration or water loss through the skin. This procedure involves the non-invasive application of a probe on the surface of the skin on the arm or leg. Affected and non-affected areas of skin will be tested. This procedure will only be performed at specified study centers. The detailed procedure for TEWL will be provided in the Study Reference Manual.

12.3.3.5. Immunohistochemistry (IHC)

Skin biopsy samples will be collected at appropriate time points defined in Appendix 1. Two punch biopsies (1 from LS and 1 from NLS) will be collected at baseline visit and one punch biopsy (from LS) at the subsequent time point. For LS, biopsy should be taken from a target lesion initially and always taken from the same lesion or location thereafter. Scar tissue from previous biopsies should be avoided. A 4.5 mm punch biopsy should be taken from the most involved chronic active erythematous, scaly lesions. For NLS, a 4.5 mm sample should be collected from the most normal appearing skin in a relative proximity to the LS biopsy site, at least 5 cm away from the lesion (at least 1 cm away, if 5 cm is not possible). Full details of sample collection, processing and storage will be outlined in a separate lab manual.

12.3.3.6. RT-PCR

Skin biopsy samples, as collected and mentioned previously will also be used for RT-PCR. The detailed methodology will be outlined in the lab manual.

12.3.3.7. Serum Soluble OX40 Ligand and Serum Soluble OX40

The PK samples will be used for the estimation of soluble OX40L and sOX40 in serum at the time points specified in the schedule of events in Appendix 1. The samples will be shipped to the specified bioanalytical lab. Serum concentrations of soluble OX40 L and OX40 will be quantified using a qualified commercial ELISA kit.

12.3.4. Pharmacogenomic Assessments

Not applicable.

12.4. Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinary laboratory values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in the Schedule of Events (Appendix 1). At the end of the study another clinical assessment consisting of a physical examination and all laboratory tests performed at the time of screening (except viral serology, and FSH) will be performed. Dosing will be based on evaluations performed by physicians/Investigator. Additional assessments can be integrated into the protocol further to investigator judgment.

12.4.1. Study Stopping Rules and Follow-up Criteria

See Section 9.3.

12.4.2. Adverse Events

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

12.4.2.1. Assessment of Adverse Event

The Reference Safety Information for this study is the IB section on Guidance for Investigators, Undesirable Effects.

12.4.2.2. Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered IP that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of an Investigational Product (IP), whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP.

Events that, while not necessarily meeting the definition of AEs, should be treated as such because they may be reportable to Regulatory Authorities according to AE reporting regulations, whether or not considered causally associated with IP, include the following:

- IP overdose, whether accidental or intentional
- IP abuse
- An event occurring from IP withdrawal
- Any failure of expected pharmacological action
- Inadvertent or accidental IP exposure (e.g., product leaking or being spilled onto a patient or care-giver)
- Unexpected therapeutic or clinical benefit from the IP
- Medication errors (i.e., incorrect route of administration, incorrect dosage, use of incorrect product).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

12.4.2.3. Assessment of Severity of Adverse Events

The severity of AEs is classified as follows:

Mild:
- The AE is a transient discomfort and does not interfere in a significant manner with the patient
- The AE resolves spontaneously or may require minimal therapeutic intervention

Moderate:
- The AE produces limited impairment of function and may require therapeutic intervention
- The AE produces no sequelae

Severe:
- The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern
- The AE produces sequelae, which require (prolonged) therapeutic intervention

The criteria for assessing severity are different from those used for seriousness (see Serious Adverse Events [Section 12.4.3] for the definition of an SAE).

12.4.2.4. Assessment of Relationship to Study Medication

The relationship of AEs to study medication is classified as follows:

Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility

Related: A causal relationship between the study treatment and the AE is a reasonable possibility

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study patient known to increase the occurrence of the event

- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

For each adverse event, the Investigator should answer the following question with Yes or No:

- Was there a reasonable possibility (evidence) that the drug caused the adverse event?

A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship.

NOTE: For patients that have not started receiving study medication the answer must be no.

12.4.3. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability/incapacity
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the Investigator to Glenmark is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

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

All SAEs must be reported to the Sponsor immediately or within 24 hours of the Investigator or their staff becoming aware of them. Reporting should be performed by recording as much information as is available at the time on the Serious Adverse Event Form and sending it to the contact information provided below:

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the Serious Adverse Event Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

Additional information will be requested by the Sponsor as necessary.

12.4.4. Pregnancy

Any patient who has a positive pregnancy test after signing informed consent should be withdrawn from the study immediately and study medication should be discontinued immediately.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy report form, immediately or within 24 hours of the Investigator learning of its occurrence. The report should contain as much information as possible and should be sent to:

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the Pregnancy Report Form should be updated with all new information and reported immediately via the same contact information above. The

pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, and this information must be sent to the Sponsor as above. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Note: Pregnancy in itself will not be considered as an AE or SAE.

Additional information will be requested by the Sponsor as necessary.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to the Sponsor.

The Investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 week of learning of the partner's pregnancy. The 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, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

12.4.5. Collection and Recording of AEs and SAEs

12.4.5.1. Collection of AEs

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of signing the informed consent form until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., IP, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Sponsor product, will be recorded from the time a patient consents to participate in the study up to and including any follow up contact. All SAEs will be reported to the Sponsor within 24 hours, as indicated in Section 12.4.3.1.

The Investigator will enquire about the occurrence of AEs/SAEs at every visit throughout the study (including Follow-up and Early Withdrawal visits where applicable), by asking the following non-leading verbal question of the patient (or care-giver, where appropriate):

- "Have you had any medical problems since your last visit?"

All Adverse Events not resolved by the end of the study or that have not resolved upon the patient's discontinuation in the study must be followed until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

12.4.5.2. Recording of AEs

All adverse events regardless of the seriousness, severity or relationship to the study medication must be recorded on the Adverse Events pages of eCRF.

Adverse events that meet the definition of a serious adverse event must be reported on the Serious Adverse Event Form provided for this study.

Adverse events must be documented in clear, unambiguous medical language. Do not use abbreviations or acronyms.

For each adverse event record only the diagnosis, do not report the characteristic signs and symptoms of the diagnosis as additional adverse events.

If a diagnosis is not available record each sign and symptom as an adverse event, when a diagnosis becomes available, update the Adverse Event Case Record Form, to record the relevant diagnosis only.

In general abnormal findings at screening should be recorded in the patient's Medical History or in the Adverse Event section of eCRF. However if, in the Investigators opinion, the finding is clinically significant and represents a condition that was not present at signing of informed consent, then the finding must be reported as an adverse event.

12.4.6. Clinical Laboratory Tests

Samples for clinical laboratory tests including hematology, chemistry, serology and urinalysis, will be taken after subjects have fasted for 4 hours and are summarized in Appendix 2.

Patients should be in a seated or supine position during blood collection. The Schedule of Events (Appendix 1) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

A central laboratory will be used to measure laboratory parameters that are to be assessed as part of the safety analyses for the CSR and to qualify patients for entry into the study. Local laboratories may be used in cases of a safety concern during the study, in which case the blood sample would be split (or 2 samples collected) to allow both a local laboratory and a central laboratory analysis. In such cases, the local laboratory result(s) will be considered part of the source documentation only and the central laboratory result will be entered into the clinical database. Local laboratory reports from non-split samples generated to follow safety concerns will be contained in the source documentation.

12.4.6.1. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

12.4.7. Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], body temperature [in centigrade]) will be obtained at the visits designated on the Schedule of Events (Appendix 1) by a validated method. Supine or semi-supine blood pressure and pulse will be measured after the patient has been resting for at least 5 minutes. All BP measurements should be performed on the same arm. At the same time, patients will be asked about their well-being, and this will also be recorded. In the event of detection of any abnormality during measurement of vital signs, the Investigator or his designate must be consulted for necessary action, which will be recorded.

12.4.8. Physical Examination

Physical examinations will be performed as designated on the Schedule of Events (Appendix 1). An abbreviated physical examination will be performed at all time-points except for screening where a full physical examination will be performed, as mentioned in Section 12.1.2. Brief clinical examination of the patient will be conducted by a qualified medical designate on duty, and as defined in the Appendix 1 of the protocol. Patient's height will be measured at screening only. In the event of detection of any abnormality during clinical examination, the Clinical Investigator must be consulted for necessary action, which will be recorded. Documentation of the physical examination will be included in the physical examination section of the eCRF. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs CRF.

12.4.9. ECG

Supine 12-lead electrocardiograms will be obtained as designated on the Schedule of Events (Appendix 1), and as per methods mentioned in the relevant SOPs and appropriate instrument user manuals. Patients must be in the supine position for a period of five minutes prior to the ECG.

A physician will have to perform a clinical assessment of each 12-lead ECG. PR, QT and QTc intervals, QRS duration and heart rate will be recorded. The QT interval will be corrected for heart rate (QTc) using Frederica's formula. A copy of the ECG tracing has to be stored as source data. Any clinically significant abnormality detected by the physician will be followed by triplicate ECGs.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see AEs [Section 12.4.2]) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs CRF.

For ECG abnormalities meeting criteria of an SAE (see SAEs [Section 12.4.3]), the site must fax or email the SAE report including the ECG report to the Sponsor using the SAE form (see Regulatory Reporting Requirements for SAEs [Section 12.4.3.1]).

12.4.10. Infusion Reactions

Infusion reactions will be characterized as either acute or delayed. Any infusion reaction occurring within 24 hours of drug infusion will be considered an acute reaction and any reaction occurring from 24 hours to 14 days following the drug infusion will be considered a delayed infusion reaction. Both types of reaction will be further characterized depending on the severity of accompanying signs and symptoms as Grade 1 to 5 as classified by Common terminology criteria for adverse events (CTCAE) Version 4.03.

Vital signs (temperature, pulse and blood pressure -systolic and diastolic) will be recorded prior to and every 30 minutes during the infusion. The patients should be stabilized prior to discharging from study site. During the infusion, patients will be monitored for the signs and symptoms of acute infusion reactions. In the event of an infusion reaction, the rate of infusion may be decreased and the duration extended at the Investigator's discretion, for patient safety. Staff trained in emergency care treatment and a facility equipped with emergency set that is readily available in the room where subjects are being dosed should be utilized for the study. Systemic hypersensitivity reactions will be managed according to treatment protocols that are in effect at the investigational site. In the absence of such a protocol, the Mount Sinai protocol for management of infusion reactions can be used.

12.4.11. Confirmation of Medical Care by Another Physician

The Investigator will instruct patients to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator/study coordinator will ask the patient whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the patient is going to receive medical care by another physician, the Investigator/study coordinator, with the consent of the patient, will inform the other physician that the patient is participating in the clinical study.

13. DATA ANALYSIS AND STATISTICAL METHODS

The statistical analysis will be coordinated by Glenmark. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized prior to the database lock at the latest. Any changes from the analyses planned in the SAP will be justified in the CSR.

All analyses will be performed using SAS® Version 9.1.3 or above.

Prior to database lock, a final blinded data review meeting will be held to allow a review of the clinical study data and to verify the data that will be used for analysis set classification. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of patients, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

The results of the study will be reported in CSR in accordance with the ICH guidance. Glenmark or delegate will prepare an integrated clinical and PK report.

13.1.1. Sample Size

No formal sample size calculation will be performed for this study. The sample size chosen is based on experience from previous studies of similar nature. Patients who are permanently discontinued from study drug due to reasons other than an AE and before the first post baseline skin biopsies (Visit 7) or before receiving two doses of study drug (Visit 7), will not be considered evaluable for the Biological Analysis Set (see Section 13.2). The sample size of 60 to 80 adult patients with AD randomized in ratio of 3: 1 (GBR 830 vs placebo) with approximately 40 evaluable patients is considered to be sufficient to provide descriptive information on the PK, safety, tolerability and potential efficacy of GBR 830.

A patient will be considered evaluable if he/she completes the Day 29 visit and has at least one post-baseline skin biopsy (Visit 7) and received two doses of study drug (Visit 7).

Details of analyses will be specified in the SAP.

13.2. Analysis Sets

Detailed criteria for analysis sets will be documented in the SAP and the allocation of patients to analysis sets will be determined prior to database hard-lock.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all patients who are randomized and received at least 1 dose of study drug.

Biological Activity Set (BAS)

The Biological Activity Set (BAS) will consist of all FAS patients who have at least one post-baseline skin biopsy (Visit 7), and received 2 doses of study drug. The primary analyses on biomarkers of disease activity obtained from biopsy will be based on the BAS.

Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all patients who took at least 1 dose of study medication, and will be used for safety analyses.

Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAF population for which sufficient serum concentration data is available to facilitate derivation of at least 1 PK parameter and for whom the time of dosing on the day of sampling is known. Additional patients may be excluded from the PKAS at the discretion of the pharmacokineticist. Any

formal definitions for exclusion of patients or time-points from the PKAS will be documented in the SAP.

13.3. Patient Disposition

Data on patient disposition (number of patients enrolled, number of drop-outs, and reasons for drop-out), demographics (gender, age, height, weight, BMI), and other baseline characteristics will be summarized. The safety, tolerability, PK, and other data from each part of the study will be listed and summarized descriptively. The number (percentage) of patients who were screened for the study (Enrolled Patients, i.e., those who signed informed consent) and reasons for screen failure will be described.

13.4. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group. Descriptive statistics will include number of patients, mean, standard deviation, minimum, median and maximum for continuous variables, and frequency and percentage for categorical variables. Continuous demographic and baseline variables include age, height and body weight, and BMI; categorical variables include gender, race, and ethnicity.

13.5. Efficacy Analyses

Analysis will be conducted on the FAS, except biomarkers of disease activity obtained from biopsy will be based on the BAS.

13.5.1. Analysis of Primary Efficacy Endpoint(s)

13.5.1.1. Primary Analysis

Expression of mRNA from skin biopsies will be analyzed using a mixed model with treatment and time as the fixed effects, and using the relevant baseline value as a covariate. Differences between treatment groups and confidence intervals will be estimated.- Summary statistics of the mRNA expression will be provided for baseline, post-baseline, and change from baseline by treatment.

13.5.2. Analysis of Secondary Efficacy Endpoint(s)

Categorical analyses will be performed on responders (e.g., percentage of patients with responding rates of 50% at the end of weeks 8 and 12). Comparisons between GBR 830 treatment and placebo groups will be done using a Cochran-Mantel-Haenszel test. For a patient, the efficacy data will be set to missing after prohibited medication is used. The last observation carried forward (LOCF) method will be used to impute missing values.

13.5.3. Analysis of Exploratory Efficacy Endpoint(s)

All exploratory efficacy analyses will be performed on the BAS for samples obtained from biopsy and FAS for samples not obtained from biopsy, and no multiplicity adjustment is planned. Analyses of exploratory endpoints will be provided in the SAP.

13.6. Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic/ Pharmacogenetic Analyses

13.6.1. Pharmacokinetic Analyses

Pharmacokinetic parameters will be summarized in tabular and graphic form. C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-tau}, and AUC_{0-t}, will be estimated after the first and last dose administrations. Parameters like $t_{1/2}$, volume of distribution, clearance and other relevant parameters may be assessed after the first and/or last dose administrations, if possible depending on the data.

Pharmacokinetic parameters will be calculated using an appropriate software program. Results of exploratory analyses will be summarized. Details will be discussed in the SAP for this study.

13.6.2. Immunogenicity Analyses

Percentage of patients with positive and negative anti-drug antibody titers will be tabulated by treatment and time point. The neutralizing antibody status would also be reported where applicable.

13.6.3. Biomarker Analyses

Informal exploratory biomarker analyses may be performed while the study is ongoing. No one involved in the day-to-day conduct of the study will have access to biomarker data before the database is locked for this study. The analysis of biomarker data will not impact any decisions regarding study conduct. Exploratory efficacy analyses will be performed on the BAS for samples obtained from biopsy, and FAS for samples not obtained from biopsy, and no multiplicity adjustment is planned. Analyses of exploratory endpoints will be provided in the SAP.

13.7. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

13.7.1. Extent of Exposure

Approximately 60 to 80 adult patients with AD are planned to be randomized in a ratio of 3 active: 1 placebo.

13.7.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to investigational product will be summarized by system organ class, preferred term and treatment group. Patients will be counted only once for each preferred term, system organ class, and by the highest severity of an event. The number and percentage of AEs by severity will also be summarized. All AEs will be displayed in listings.

13.7.3. Laboratory Values

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts in laboratory tests relative to normal ranges from baseline to each time point during treatment will also be tabulated. All laboratory data will be displayed in listings.

13.7.4. Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Values of potential clinical significance will be tabulated. All vital signs data will be displayed in listings.

Shift tables will present changes from baseline (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment (or end of phase or by visit).

13.7.5. Electrocardiograms

All ECG variables will be presented by visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment (or end of phase or by visit).

13.7.6. Physical Examination

Descriptive statistics will be used to summarize findings of potential clinical significance and will be listed.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or designee will implement and maintain quality assurance and quality control systems with Standard Operating Procedures (SOP) to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance to the protocol, GCP standards, ICH and other applicable local regulations.

The Sponsor is responsible for securing agreement among collaborating parties to ensure direct access to clinical-study-related sites and material to ensure that all data are reliable and have been processed correctly.

14.1. Procedures for Monitoring Compliance

To ensure the completeness and accuracy of case report forms, the study will be monitored by a designated Clinical Trial Monitor (CTM). At regular intervals the study monitor will visit the study center(s), the frequency of which will vary depending on the recruitment rate. The first monitoring visit will be conducted after the first few patients are enrolled. It is the duty of the Investigator to provide open access to the monitor of all study related records at previously agreed times. The Sponsor, IRB/IEC, and regulatory authorities shall have right to direct access to source data for verification.

14.2. Inspection

An inspection is defined as the act of a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and or CRO facilities or any other establishments deemed appropriate by the regulatory authorities.

14.3. Audit

An audit is a systematic and independent review of study-related activities and documents to determine whether study-related activities were conducted and the data were accurately recorded and analyzed according to the protocol, SOPs, GCP, and the appropriate requirements.

In conducting this study the Investigator accepts that the Sponsor, IRB/IEC or regulatory body may, at any time by appointment, conduct an audit of the study site.

15. ETHICS

15.1. Ethics Committee Approval

The clinical study protocol, ICF, and any documents that are given to the study patients (questionnaires, diaries, etc.) must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with Section 3 of ICH E6 (GCP) and any local regulations. Any protocol amendment, or revision to the ICF or other documents used in the study, will be resubmitted to the IRB/IEC for review and approval. Documentation of IRB/IEC compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

Any queries raised by the IRB/IEC in regard to the study will be provided in writing to the Investigator or Sponsor, depending on local regulatory obligations. The Investigator or Sponsor,

depending on local regulatory obligations, will be responsible for providing answers and resolving all queries prior to study start.

A signed letter of study approval from the IRB/IEC chairman must be sent to the Investigator or Sponsor, depending on local regulatory obligations, before study start and the release of any investigational product to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the Investigator or Sponsor, depending on local regulatory obligations.

Written approvals from the IRB/IEC and Regulatory Authority must be obtained before starting the informed consent process for the first patient at the site. The IRB/IEC will also review the ICF and endorse it in writing.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IECs (or if regionally required, the Investigator and the relevant IRB/IEC via the head of the medical institution) of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IECs with a brief report of the outcome of the study, if required.

At the end of the study, the Investigator or Sponsor should notify the IRB/IEC and Regulatory Authority in accordance with local regulatory obligations. The end of the study will be the date of the last study visit for the last patient in the study. The Investigator or Sponsor, depending on local regulatory obligations, should also provide the IEC/IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the Investigator or Sponsor should notify the IRB/IEC and Regulatory Authority in accordance with applicable regulatory requirements, and a detailed written explanation of the reasons for the termination/halt should be given.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with SOPs of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- The ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed patient consent and IRB/IEC regulations and applicable sections of US 21 CFR Part 312
- The regulations in the Food and Drug act in Health Canada
- A waiver from the [IRB(s)/IEC(s)] will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.

15.3. Informed Consent Process

The Investigator is responsible for obtaining informed consent from each patient/legally acceptable representative (LAR) participating in the study. All pertinent aspects of the study must be explained to the patient/LAR before he or she signs the informed consent. Informed consent must be obtained from the patient/LAR before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of the study medication. Each patient must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The patient/LAR should understand the statement before signing and dating it and will be given a copy of the signed document.

Each patient must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each patient will be verified by the Sponsor or designee and kept on file according to local procedures at the site.

The patient or the patient's LAR should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented. If required, informed consent should be obtained using an amended ICF for the patient's continuation in the study.

15.4. Approval of the Protocol and Amendments

Patients will not be admitted to the study before approval of the study protocol and other relevant study documents by the IRB/IEC and Regulatory Authority.

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor, Principal Investigator and IRB/IEC before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation or the scientific quality of the study will require additional approval by the IRB/IEC and the Regulatory Authority.

These requirements for approval will in no way prevent any immediate action from being taken by the Principal Investigator in the interests of preserving the safety of the patients included in

the study. If an immediate change to the protocol is felt necessary by the Principal Investigator and is implemented for safety reasons the IRB/IEC will be informed within 15 working days.

Protocol amendments that affect only administrative aspects of the study may not require submission to Health or Regulatory Authority. However, the IRB/IEC, according to local obligations will either approve all amendments to the protocol or will be notified of all the changes. In these cases, the Investigator will inform the IEC of such changes.

15.5. Protocol Deviation

Any deviation from the protocol will be recorded as a protocol deviation.

16. DATA HANDLING AND RECORD KEEPING

16.1. Data Management

Data from the study will be managed by Glenmark Pharmaceuticals Ltd or their representative. A copy of the study results will be made available to the clinical investigator for review.

All data will be recorded on Electronic Case Report Forms (eCRFs). The Investigator will allow representatives of the Sponsor, regulatory agencies, and their designees to inspect all study documents (including, but not limited to, consent forms, investigational product accountability forms, IRB/IEC approvals) and pertinent hospital or clinic records for confirmation of data throughout and after completion of the study. Monitoring visits will be conducted as needed during the course of the study. A complete review of source documentation of key efficacy and safety data will be conducted at each monitoring visit for verification that all information recorded in the CRF accurately reflects the data recorded in the patient's source documents.

All data verification, using hospital or clinic records, will be performed respecting patient confidentiality and will be carried out in accordance with Standard Operating Procedures (SOPs). An electronic copy of the study eCRF will be provided to the investigational site upon final query resolution and Database closure.

All patient data generated during the study will be recorded and transcribed in the eCRF. The Principal Investigator must approve the eCRF to confirm eligibility. The final authorization of the CRF data is the Investigator Signature form. This form must be approved by the Principal Investigator to signify that he/she has reviewed the eCRF, including all laboratory and safety assessments, and that all of the data therein is complete and accurate.

The data will be reviewed to ensure that the forms were completed properly and that all data has the correct patient identification number throughout.

16.2. Direct Access to Source Data/Documents

Essential demographic data will be documented both within the patient’s hospital record notes (source data) and within the trial eCRF and be available for inspection by the Sponsor’s CTM.

Source data will also include date of consent, time of drug administration and blood sampling, together with vital signs recorded at each visit.

It is the responsibility of the Investigator/s to maintain accurate and up to date records of all clinical study related activities, which should be entered on the eCRFs provided. The source documents should be made available to the CTM on request, and in the event of a formal Investigator site audit.

16.3. Confidentiality and Intellectual Property

All information disclosed to the Investigator by the Sponsor or persons assigned by the Sponsor shall be treated by the Investigator as strictly confidential. The Investigator shall only use such information for the purpose of conducting the clinical study described in this protocol and agrees not to disclose such information to any third party except those of his/her colleagues and employees who are assisting in the conduct of the study and who are bound by the obligations of confidentiality.

Information concerning the investigational product, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the Investigator understands that he has an obligation to provide the Sponsor with all data obtained during the study. The Institution and/or the Investigator undertake that they will not reverse-engineer, decompile or dissemble the information or make any variant out of the information.

All intellectual property arising out of, or in connection with, the conduct of the clinical study described in this protocol ("Derivative Intellectual Property") shall be promptly disclosed to the Sponsor. Any such Derivative Intellectual Property shall be the sole property of the Sponsor. The Institution and/or the Investigator, its affiliates and any person claiming through them shall do all acts and things as shall be necessary to vest all right, title and interest therein in the Sponsor. The Institution and/or the Investigator shall keep the said Derivative Intellectual Property confidential in accordance with this Agreement.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

16.4. Record Retention

On completion of the study electronic copies of all eCRFs (if generated) or the paper copies of the eCRF will be provided to the Investigator site for safekeeping for the duration stipulated by ICH GCP (currently 25 years or last marketing authorization, whichever is later).

17. FINANCING AND INSURANCE

The Sponsor will provide insurance for any patients participating in the study in accordance with all applicable laws and regulations.

18. PUBLICATION POLICY

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (e.g., what, when, where, etc.) will be mutually agreed upon by the Investigator and Sponsor. However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is patient to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

19. DISCONTINUATION OF STUDY

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

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APPENDIX 1. SCHEDULE OF EVENTS

Visit[1]	Screen-ing	Base-line visit	Follow-up visits				Dosing visit	Follow-up visits						
Study Day	**-30 to -1**	**1**	**4±1**	**8±1**	**15±1**	**22±2**	**29±1**	**32±1**	**36±1**	**43±1**	**50±2**	**57±2**	**71±2**	**85±2**
Visit ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed consent	X													
Medical history[2]	X													
Demographics (incl. height, weight and BMI)[3]	X	X					X							X
Physical examination[4]	X	X			X		X			X				X
TB testing[5]	X													
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[7]	X	X	X	X			X	X	X			X	X	X
Clinical laboratory[8]	X	X	X	X			X	X	X			X	X	X
Drug and alcohol screen[9]	X	X					X							
HBsAg, Anti-HBcAg, HCV and HIV tests	X													
Serum pregnancy (females only)[10]	X	X												X
Urine pregnancy (females only) [11]		X					X							
EASI, SCORAD, IGA, BSA [12,13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole body photography[12]		X		X						X				X
DLQI, NRS		X	X	X	X	X	X	X	X	X	X	X	X	X

Visit[1]	Screen-ing	Base-line visit	Follow-up visits				Dosing visit	Follow-up visits						
Study Day	**-30 to -1**	**1**	**4±1**	**8±1**	**15±1**	**22±2**	**29±1**	**32±1**	**36±1**	**43±1**	**50±2**	**57±2**	**71±2**	**85±2**
Visit ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Withdraw medication & dispense diary[14]	X													
Inclusion/exclusion criteria	X	X												
Randomisation[15]		X												
Study drug administration[16]		X					X							
Previous and concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling for GBR 830[17]		X	X	X	X	X	X	X	X	X	X	X	X	X
Leukocyte sub-population cell counts, TEWL, total IgE, eosinophil [18]		X		X	X		X		X	X		X	X	X
Cytokines and exploratory analysis[18]		X					X						X	
Immunogenicity samples[19]		X			X		X					X		X
Skin biopsies[20]		X					X						X	
Adverse events[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone call[22]		X					X							

Appendix 1– Footnotes

1. Visits do not include a Day 0. Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results). On visits patients should fast for at least 4 hours prior to safety sample collection. The last assessments done prior to dosing will be considered as baseline. The last follow-up visit on Day 85 will be considered the end-of study. The end of study assessments will be done in place of visit procedures, for all patients receiving the study medication for all early withdrawal and dropouts. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.
2. Medical history includes recent medical history (any illness occurring within past 4 weeks), previous medical history (only significant medical or surgical illness), smoking, alcohol and intake of drugs of abuse)

3. Demographics: includes date of birth, gender, race and ethnicity, height and body weight. BMI will be calculated as weight (kg) / [height (m) x height (m)]. Only body weight will be repeated at subsequent visits. Height measured at screening will be used for calculation of BMI at subsequent visits
4. Physical examination: Comprehensive examination at screening and brief examination at all subsequent visits.
5. TB testing: Patients must test negative for a QuantiFERON Gold-TB test done at screening;
6. Vital signs: includes supine or semi-supine BP and pulse; and body temperature at screening, within 30 minutes before administration, 0.5 ± 10 mins during infusion, 1.0 ± 10 mins, 2.0 ± 10 mins and 6.0 hours ± 10 mins estimated from the end time of the first infusion, and within 30 minutes before administration, 0.5 ± 10 mins during infusion, 1.0 ± 10 mins, 2.0 ± 10 mins and 3.0 hours ± 10 mins estimated from the end time of the second infusion and at each follow-up visit. Vitals have to be monitored every half hour during infusion.
7. A single ECG will be taken at screening, at pre-dose, 2 ± 30 mins and 6 hours ± 30 mins estimated from the end time of the first infusion, at pre-dose, 2 ± 15 mins and 3 hours ± 15 mins estimated from the end time of the second infusion, and on Day 4, Day 8, Day 32, Day 36, Day 57, Day 71 and on Day 85. A triplicate ECG will be taken if there are any clinically significant abnormalities detected by the physician in single ECG.
8. Clinical laboratory tests (labs) include hematology, biochemistry and urinalysis after a 4-hour fast. Detailed panel mentioned in Appendix 2. Labs will be done at screening, Day 1 (pre-dose), Day 4, Day 8, Day 29 (pre-dose), Day 32, Day 36, Day 57, Day 71 and Day 85. Serum FSH and viral serology will be done only at screening.
9. Drug and alcohol screen: alcohol or drugs of abuse at screening and before administration of each dose (pre-dose). Drug screen includes amphetamines, BZD, barbiturates, cocaine, opioids, and cannabinoids.
10. Serum pregnancy test for all women will be done during screening, Day 1 and at the end of study.
11. Urine pregnancy test for all women will be done before administration of each dose (pre-dose). Results of the pregnancy test should be negative before dispensing of study drug(s)
12. Efficacy assessments will be done by a trained, blinded assessor. The same assessor should do the assessments of a particular patient throughout the study. Assessments will be done at screening, at baseline (pre-dose on Day 1), at Days 4, 8, 15, 22, 29 (pre-dose), 32, 36, 43, 50, 57, 71, and 85. If the patient signs for optional consent for photography, whole body photography (from neck down-anterior and posterior), will be taken, at baseline and at Days 8, 43, and 85.
13. BSA will be done by the same assessor performing other efficacy assessment, and at similar time points.
14. Patient must enter data into the diary every day from start of screening period to end of study visit. Patient will be trained on the use of diary. Patient will be instructed to enter the data every morning at a designated time and how to record them.
15. Day of randomization and first dosing are assumed to be same, no waiver allowed. Randomization schedule will be prepared using a centralized computer-based IVRS/IWRS system.
16. IP administration: Continuous slow IV infusion for 60 min. The infusion volume must be calculated using the patient's current body weight. The study site will contact patients by telephone approximately 24 hours after each infusion of IP.
17. Serum samples for GBR-830 PK analysis will be obtained within 15 minutes before administration of each dose (pre-dose), immediately at the end of each infusion ± 10 mins; at 1.5 ± 10 mins, 2 ± 10 mins, 4 ± 10 mins hours estimated from the start time of infusion, 72, 168, 336, 504 hours after each infusions; and on Day 57 (1344 hours), 71 (1680 hours), and 85 (2016 hours) estimated from the start time of first infusion. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.
18. Leukocyte sub-population cell counts, TEWL, total IgE, eosinophil will be done on Day 1, 8, 15, 29, 36, 43, 57, 71, and 85. Samples for TARC, eotaxin-3, and cytokine panel and additional exploratory analysis will be taken at baseline, at Day 29, and Day 71. TEWL assessment is being performed by sites as per the TEWL manual and a predefined time point as per protocol will not be applicable.
19. Samples will be collected for immunogenicity analysis at pre-dose, and at Day 15, (pre-dose) Day 29, Day 57, and Day 85.
20. Skin biopsies will be taken at baseline at Day 29, and Day 71.

21. Adverse events will be reported as described and classified in the CTCAE version 4.03. At each visit, the Investigator will ask the patient whether he/she has received medical care by another physician since the last visit or is planning to do so in the future.
22. The site will contact the subject 24 hours after each infusion by phone.

APPENDIX 2. LIST OF CLINICAL LABORATORY TESTS

The following tests will be performed. Clinical evaluation of all clinical laboratory data will be performed by a qualified physician. Reference range values from the central lab will be used for the tests mentioned below.

<table>
<tr><td>HEMATOLOGY</td><td colspan="2">SERUM BIOCHEMISTRY</td></tr>
<tr><td>• Hemoglobin
• Hematocrit
• White blood cell count
• Differential white cell count
• Red blood cell count with mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration
• Platelets</td><td rowspan="2">Electrolytes
• Sodium
• Potassium
• Calcium
• Chloride
• Bicarbonate

Liver function tests
• Total and direct bilirubin
• Total protein
• Globulin
• Albumin
• AST
• ALT
• GGT
• ALP (Alkaline phosphatase)
• Lactate dehydrogenase</td><td rowspan="2">Renal function tests
• Creatinine
• Blood urea nitrogen (BUN)

Other
• Fasting blood sugar
• Serum FSH (all women, only at screening)
• Serum and urine Beta-HCG (for females only)
• Serum Immunoglobulins

Lipid Profile
• Total cholesterol
• Triglycerides
• HDL
• LDL
• VLDL</td></tr>
<tr><td>URINALYSIS

• pH
• Specific gravity
• Glucose
• Protein
• Ketones
• Blood
• Bilirubin
• Leukocyte Esterase
• Nitrite
• Routine Microscopy</td></tr>
<tr><td>SEROLOGY
• Hepatitis B (HBsAg)
• Anti-Hepatitis B Core (Anti-HBcAg)
• Hepatitis C antibody
HIV 1 and 2</td><td colspan="2">OTHER
• QuantiFERON Gold Blood TB Test
• total IgE
• circulating eosinophil counts</td></tr>
</table>

Table for Biopharmaeutics Analyses

Serum GBR 830	serum soluble OX40 ligand (sOX40L)
Anti-drug antibodies	serum soluble OX40 (sOX40)

Table for Cytokine, Flow Cytometry and Biomarker Panels

Cytokine and chemokine panel	
Serum cytokines and chemokines: IL-22 (tested by Singulex), IL-13, CCL17 (TARC = thymus and activation-regulated chemokine), Eotaxin (CCL11), TSLP, CXCL10 (IP-10), CCL2 (MCP-1), CCL20 (MIP3A),CCL22 (MDC), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL13 (MCP-4), CXCL11 (IP-9; I-TAC), and CXCL9 (MIG) (tested by OLINK multiplex panels).	
Antigen Marker(s)	**Cell Population Identified**
Single panel	
CD45RO -CD3 – CD4 – CD8 – OX40 – GBR830 – CD127 – CD25.	Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells
IHC Panel (skin) & Skin thickness	
Skin thickness: Hematoxylin and Eosin staining Epidermal hyperplasia: Keratin 16 Epidermal hyperplasia: Ki67 Infiltrating T cells: CD3 and OX40 High affinity IgE receptor; inflammatory dendritic cells: FcEpsilonRI; eosinophils; MBP Atopic DCs: OX40L	
RT-PCR panel (skin RNA), including at least but not limited to:	
~~hARP,~~ K16, IL-13, IL-17A, IL-22, IFNg, OX40L, IL23p40, IL23p19	

APPENDIX 3. NAME(S) OF CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND/OR FACILITIES PARTICIPATING IN THE STUDY

Clinical conduct and reporting	**Clinical laboratory**
Innovaderm Research Inc. 1851, Sherbrooke St. East, Suite 502 Montréal, QC H2K 4L5 Canada	Quintiles Laboratory, US
Biopharmaceutical analysis	**Exploratory analysis**
Nuvisan GmbH Biopharmaceutics Wegenerstraße 13 89231 Neu-Ulm Germany	Icahn School of Medicine at Mount Sinai 1425 Madison Avenue Icahn 13-76, New York, NY 10029

APPENDIX 4. SUMMARY OF CHANGES IN CURRENT PROTOCOL AMENDMENT

PROTOCOL NUMBER: GBR 830-201

PROTOCOL AMENDMENT 3.0

SUMMARY OF CHANGES

A Phase IIa, Double-Blind, Randomized, Placebo-controlled,
Exploratory Study to Evaluate the Safety, Biological Activity and Pharmacokinetics
of GBR 830 in Adult Patients With Moderate-to-Severe Atopic Dermatitis

PROTOCOL HISTORY

PROTOCOL VERSION 1.0, 12-Oct-2015

PROTOCOL VERSION 2.0, 19-May-2016

PROTOCOL VERSION 3.0, 07-Nov-2016

PROTOCOL VERSION 4.0, 16-Feb-2017

Description of Changes in Protocol Version 4.0 (Amendment 3.0) dated 16-Feb-2017

Minor editorial changes for accuracy, clarity, and consistency and minor formatting changes have been made throughout the document and are not included in the description(s) below.

Key: **Bold:** Newly added text
~~Strikethrough text~~: Deleted text from the previous version of the protocol.

A. Details of Substantial Changes to the Protocol

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
1. Synopsis, Study Objective(s); Section 6.2, Secondary Objective(s)		
Used to read: Secondary: • Effect of GBR 830 on additional efficacy parameters in adult patients with AD.	Now reads: Secondary: • Effect of GBR 830 on ~~additional~~ **clinical** efficacy parameters in adult patients with AD.	Clarification that secondary efficacy parameters are clinical.
2. Synopsis, Study Endpoint(s); Section 8.3, Exploratory Endpoint(s)		
Used to read: Exploratory: Change from baseline in levels of: • Cytokines in serum: Interleukin (IL)-13 and IL-22, Chemokine ligands (CCL) CCL2, CCL3, CCL4, CCL5, CCL18, CCL20, CCL22, CCL13, CXCL9, CXCL10, CXCL11 • Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells, OX40 T cells, GBR 830 T cells). • Cellular infiltrates (T-cells, Dendritic cells) as assessed by CD3, FcEpsilon RI and OX40L. • Serum Thymus and activation-regulated chemokine (TARC/CCL17), eotaxin-3, total Immunoglobulin E (IgE), and circulating eosinophil counts • Percentage OX40 receptor occupancy (RO)	Now reads: Exploratory: Change from baseline in levels of: • ~~Cytokines in serum: Interleukin (IL) 13 and IL 22, Chemokine ligands (CCL) CCL2, CCL3, CCL4, CCL5, CCL18, CCL20, CCL22, CCL13, CXCL9, CXCL10, CXCL11~~ **Cytokines and chemokines in serum: Interleukin (IL)-22, IL-13, chemokine ligand (CCL)-17 (TARC = thymus and activation-regulated chemokine), Eotaxin (CCL11), TSLP, CXCL10 (IP-10),CCL2 (MCP-1), CCL20 (MIP3A), CCL22 (MDC), CCL3 (MIP-1α, CCL4 (MIP-1β), CCL13 (MCP-4), CXCL11 (IP-9; I-TAC) and CXCL9 (MIG).** • Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells~~, OX40 T cells, GBR 830 T cells~~). • Cellular infiltrates (T-cells, **d**endritic cells) as assessed by CD3, FcEpsilon RI, ~~and~~ OX40L**, OX40, and MBP**.	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
	• Serum ~~thymus and activation regulated chemokine (TARC/CCL17), eotaxin-3,~~ total Immunoglobulin E (IgE), **serum soluble OX40, serum soluble OX40 ligand (sOX40L),** and circulating eosinophil counts • ~~Percentage OX40 receptor occupancy (RO)~~	
3. Synopsis, Biomarker Assessments		
Used to read: RO assay, cytokines, TEWL, TARC, eotaxin-3, total IgE, eosinophil levels will also be measured in the study.	Now reads: **Leukocyte sub-population cell counts** ~~RO assay~~, cytokines, **chemokines**, TEWL, ~~TARC, eotaxin-3,~~ total IgE, **sOX40L, and** eosinophil levels will also be measured in the study. **Cellular infiltrates (T-cells, dendritic cells) will be assessed by immunohistochemistry of biopsy slides with CD3, FcEpsilon RI, OX40L, OX40, and MBP.** **Serum soluble OX40 and OX40L will be measured using PK samples at the time points defined in Appendix 1.**	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review. Clarified that serum soluble OX40 and OX40 ligand will be measured from PK blood samples taken.
4. Section 11.2, Dosing visits (Visits 2 and 7); Section 11.4, Follow-up Visits 4 and 9 (Days 8±1 and 36±1); Section 11.5, Follow-up Visits 5 and 10 (Days 15±1 and 43±1); Section 11.7, Follow-up Visits 12 and 13 (Days 57±2 and 71±2); Section 11.8, Follow-up Visits (end of study) assessments on Day 85 (±2); Appendix 1 Schedule of Events (table row and footnote 18)		
Used to read: • RO assay, TEWL, total IgE, eosinophil count	Now reads: • ~~RO assay~~, **Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, Tregs, Memory T cells),** TEWL, total IgE, eosinophil count	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.
5. Section 12.3.3.1, title of section		
Used to read: 12.3.3.1 Flow cytometry/ Receptor Occupancy assay	Now reads: 12.3.3.1 Flow cytometry/ ~~Receptor Occupancy assay~~ **Leukocyte sub-population cell counts**	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.
6. Section 12.3.3.2, title of section		

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
Used to read: 12.3.3.2 Cytokine	Now reads: 12.3.3.2 Cytokine**s and Chemokines**	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.
7. Former Section 12.3.3.3, TARC (CCL17)		
Used to read: Thymus and activation-regulated chemokine is a chemokine, shown to be strongly associated with disease severity in AD, and may be involved in pathogenesis of the disease. Baseline TARC levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of GBR 830 on TARC. Detailed instructions for blood sample collection will be outlined in a separate lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.	Section 12.3.3.3 deleted entirely ~~Section 12.3.3.3, TARC (CCL17)~~ ~~Thymus and activation-regulated chemokine is a chemokine, shown to be strongly associated with disease severity in AD, and may be involved in pathogenesis of the disease. Baseline TARC levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of GBR 830 on TARC. Detailed instructions for blood sample collection will be outlined in a separate lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.~~	Deleting section 12.3.3.3 since TARC is included in a previous section.
8. Former Section 12.3.3.4, Eotaxin 3 (CCL26)		
Used to read: Eotaxin-3 is a chemokine, shown to be associated with disease severity in AD, and may be involved in pathogenesis of the disease. Baseline eotaxin-3 levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of GBR 830 on eotaxin-3. Detailed instructions for blood sample collection will be outlined in a separate lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.	Section 13.3.3.4 deleted entirely ~~Section 12.3.3.4, Eotaxin 3 (CCL26)~~ ~~Eotaxin-3 is a chemokine, shown to be associated with disease severity in AD, and may be involved in pathogenesis of the disease. Baseline eotaxin-3 levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of GBR 830 on eotaxin-3. Detailed instructions for blood sample collection will be outlined in a separate lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.~~	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review. (Eotaxin-3 will not be measured as it is not on the OLINK panels.)

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
9. Section numbers 12.3.3.3, 12.3.3.4, 12.3.3.5 (formerly 12.3.3.5, 12.3.3.6, 12.3.3.7)		
Used to read: 12.3.3.5 Total IgE 12.3.3.6 Transepidermal Water Loss 12.3.3.7 Immunohistochemistry (IHC)	Now reads: ~~12.3.3.5~~**12.3.3.3** Total IgE ~~12.3.3.6~~**12.3.3.4** Transepidermal Water Loss ~~12.3.3.7~~**12.3.3.5** Immunohistochemistry (IHC)	Renumbering of subsections due to deletion of TARC and Eotaxin subsections above (see points 7 and 8 in this table).
10. Section 12.3.3.6 (formerly 12.3.3.8), RT-PCR		
Used to read: 12.3.3.8, RT-PCR and gene microarray Skin biopsy samples, as collected and mentioned previously will also be used for RT-PCR. The detailed methodology will be outlined in the lab manual.	Now reads: 12.3.3.6, RT-PCR ~~and gene microarray~~ Skin biopsy samples, as collected and mentioned previously will also be used for RT-PCR ~~and gene microarray~~. The detailed methodology will be outlined in the lab manual.	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.
11. Section 12.3.3.7, Serum Soluble OX40 Ligand and Serum Soluble OX40		
Used to read: (Section not applicable)	**New section 12.3.3.7 added:** **The PK samples will be used for the estimation of soluble OX40L and sOX40 in serum at the time points specified in the schedule of events in Appendix 1. The samples will be shipped to the specified bioanalytical lab. Serum concentrations of soluble OX40 L and OX40 will be quantified using a qualified commercial ELISA kit.**	Addition of serum soluble OX40 and serum soluble OX40L and clarification of when samples will be collected.

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
12. Section 13.5.1.1, Primary Analysis		
Used to read: All continuous efficacy variables will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the fixed effects, and using the relevant baseline value as a covariate. Differences between treatment groups and confidence intervals will be estimated within the framework of ANCOVA. In the event that the model assumptions are not warranted, the rank-based ANCOVA will be used.	Now reads: ~~All continuous efficacy variables~~ **Expression of mRNA from skin biopsies** will be analyzed using ~~an analysis of covariance (ANCOVA)~~ a **mixed** model with treatment **and time** as the fixed effects, and using the relevant baseline value as a covariate. Differences between treatment groups and confidence intervals will be estimated ~~within the framework of ANCOVA~~. ~~In the event that the model assumptions are not warranted, the rank-based analysis of covariance (ANCOVA) will be used.~~ **Summary statistics of the mRNA expression will be provided for baseline, post-baseline, and change from baseline by treatment.**	Updated statistical methods to be used in the primary analysis, to better reflect the primary objectives.
13. Section 13.5.2, Analysis of Secondary Efficacy Endpoint(s)		
Used to read: Categorical analyses will be performed on responders (e.g., percentage of patients with responding rates of 50% at the end of week 12).	Now reads: Categorical analyses will be performed on responders (e.g., percentage of patients with responding rates of 50% at the end of week**s 8 and** 12).	Clarification that analyses will be performed using both week 8 and week 12 data.
14. Appendix 2, List of Clinical Laboratory Tests		
Used to read: OTHER • QuantiFERON Gold Blood TB Test • Serum TARC • eotaxin-3 • total IgE • circulating eosinophil counts	Now reads: OTHER • QuantiFERON Gold Blood TB Test • ~~Serum TARC~~ • ~~eotaxin-3~~ • total IgE • circulating eosinophil counts	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
15. Appendix 2, Table for Biopharmaceutic Analyses		
Used to read: (Table for Biopharmaceutic Analyses not applicable.)	Added: **Table for Biopharmaceutic Analyses** • **Serum GBR 830** • **Serum soluble OX40 ligand (sOX40L)** • **Anti-drug antibodies** • **Serum soluble OX40 (sOX40)**	Added sOX40L and sOX40. Clarification of testing to be performed by Biopharmaceutics Laboratory listed in Appendix 3.
16. Appendix 2, Table for Cytokine, Flow Cytometry, and Biomarker Panels		
Used to read: Cytokine panel Serum Cytokines (IL-13, IL-22, by singulex platform and a panel of 10 Th1 and Th2 chemokines by MSD (CCL2, CCL3, CCL4, CCL5, CCL18, CCL20, CCL22, CCL13, CXCL9, CXCL10, CXCL11 RO assay panel … Total T, T helper, Cytotoxic T, Tregs, Memory T cells, OX40 T cells, GBR 830 T cells … Infiltrating T cells: CD3 High affinity IgE receptor; inflammatory dendritic cells: FcEpsilonRI . . . Gene microarray panel Affymetrix U133Plus 2 arrays RT-PCR panel (skin RNA) hARP, K16, IL-13, IL-17A, IL-22, IFNg, OX40L, IL23p40, IL23p19	Now reads: Cytokine **and chemokine** panel ~~Serum Cytokines (IL-13, IL-22, by singulex platform and a panel of 10 Th1 and Th2 chemokines by MSD (CCL2, CCL3, CCL4, CCL5, CCL18, CCL20, CCL22, CCL13, CXCL9, CXCL10, CXCL11~~ **Serum cytokines and chemokines: IL-22 (tested by Singulex), IL-13, CCL17 (TARC = thymus and activation-regulated chemokine), Eotaxin (CCL11), TSLP, CXCL10 (IP-10), CCL2 (MCP-1), CCL20 (MIP3A),CCL22 (MDC), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL13 (MCP-4), CXCL11 (IP-9; I-TAC), and CXCL9 (MIG) (tested by OLINK multiplex panels)** ~~RO assay panel~~ ~~…~~ Total T, T helper, Cytotoxic T, Tregs, Memory T cells~~, OX40 T cells, GBR 830 T cells~~ … Infiltrating T cells: CD3 **and OX40** High affinity IgE receptor; inflammatory dendritic cells: FcEpsilonRI**; eosinophils; MBP** **. . .**	Revised to reflect actual biomarkers being analyzed based on update of the technical feasibility review.

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
	~~Gene microarray panel~~ ~~Affymetrix U133Plus 2 arrays~~ RT-PCR panel (skin RNA) **, including at least but not limited to:** ~~hARP,~~ K16, IL-13, IL-17A, IL-22, IFNg, OX40L, IL23p40, IL23p19	

B. Details of Non-substantial Changes to the Protocol:

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
1. Section 7, Figure 2, Study Flow Chart; Section 11, Window for collection of samples for GBR-830 PK analysis, window for vital signs, window for ECG recording, For all other safety and pharmacodynamics/biomarker/immunogenicity assessments; Appendix 1, Schedule of Assessments (footnote 17)		
Used to read: If the second infusion time is altered, then the time-points for visits V12, V13 and V14 will be calculated from the second infusion.	Now reads: ~~If the second infusion time is altered, then the time-points for visits V12, V13 and V14 will be calculated from the second infusion~~**. Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.**	Clarification that assessments following the nomimal Day 29 dose will be calculated from the actual day/start time of this second dose.
2. Section 7.2, Discussion of Study Design, Including Choice of Control Groups		
Used to read: . . . Recently, improvements of the AD molecular signature were observed in patients after treatment with 4 weeks with cyclosporine and dupilumab Guttman-Yassky E et al; Hamilton et al, 2014), a targeted Th2 antagonist, and these changes occurred earlier and were larger than clinical endpoints, suggesting that these are valid endpoints for an exploratory study.	Now reads: . . . Recently, improvements of the AD molecular signature were observed in patients after treatment with ~~4 weeks with cyclosporine and~~ dupilumab ~~Guttman-Yassky E et al;~~ Hamilton et al, 2014; **Beck et al, 2014**), a targeted Th2 antagonist, and these changes occurred earlier and were larger than clinical endpoints, suggesting that these are valid endpoints for an exploratory study.	Correction of typographical error.
3. Section 10.3, Allocation to Treatment Groups		
Used to read: • For patients randomized prior to amendment 3 who do not	Now reads: • For patients randomized prior to **protocol version 3 (amendment**	Correction of typographical error.

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
complete at least the Day 29 visit: . . . • For patients randomized after amendment 3 who do not complete at least the Day 29 visit: . . .	~~32)~~ who do not complete at least the Day 29 visit: . . . • For patients randomized after **protocol version 3 (amendment ~~23)~~** who do not complete at least the Day 29 visit: . . .	
4. Section 11.9, Early Withdrawal Visit		
Used to read: The Early Withdrawal Visit will be performed as applicable (see Section 9.3.2 for additional information). The end of study assessments will be performed for all patients receiving study drugs who withdraw prematurely from the study. Any patient who is withdrawn must be followed-up for approximately 5 half-lives (56 days) after the last infusion.	Now reads: The Early Withdrawal Visit will be performed as applicable (see Section 9.3.2 for additional information). The end of study assessments will be performed for all patients receiving study drugs who withdraw prematurely from the study. Any patient who is withdrawn must be followed-up **as outlined in Section 9.3 and in Appendix 1, but at least** for approximately 5 half-lives (56 days) after the last infusion.	Clarification of end of study assessments in the event a subject withdraws early from the study.
5. Section 12.4.4, Pregnancy		
Used to read: Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy form, . . .	Now reads: Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy **report** form, . . .	Minor clarification of name of form.

From Protocol Version 3.0 (Amendment 2.0) 07-Nov-2016	To Protocol Version 4.0 (Amendment 3.0) 16-Feb-2017	Rationale for Amendment
6. Section 13.6, Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic/Pharmacogenetic Analyses		
Used to read: 13.6 . . . 13.6.1.1 . . . 13.6.1.2 . . . 13.6.1.3 . . .	Now reads: 13.6 . . . 13.6.1 . . . 13.6.2 . . . 13.6.3 . . .	Correction of typographical error in numbering subsections.
7. Section 20, References		
Used to read: (References 1 – 22.) Reference 13: Jennifer et al. . . .	Now reads: (References 1-22 updated to put into Vancouver style, cross-references fixed in document where applicable.) Reference 13: Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. . . .	References 1-22 updated to put into Vancouver style. Cross-references fixed in document where applicable. Reference 13 corrected typographical error in first author name (Jennifer D. Hamilton).
8. Appendix 1, Schedule of Assessments (footnote 1)		
Used to read: 1. . . . Assessments done in relation to the second infusion will be calculated from the actual day of dosing.	Now reads: 1. ~~**Assessments done in relation to the second infusion will be calculated from the actual day of dosing.**~~ **Visits and assessments done in relation to the second infusion will be calculated from the actual day/start time of the second infusion. This applies to V8 to V11, inclusively. For V12, V13, and V14, the time points for assessment will be 672hr, 1008hr, and 1344hr, respectively, from the start time of the second infusion.**	Clarification that assessments following the nomimal Day 29 dose will be calculated from the actual day/start time of this second dose.

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9. Appendix 1, Schedule of Assessments (footnote 18)		
(Not applicable)	Added to footnote 18: 18. . . . **TEWL assessment is being performed by sites as per the TEWL manual and a predefined time point as per protocol will not be applicable.**	Clarification that TEWL assessment is to be performed as per the TEWL manual.
10. Appendix 4, title of appendix and contents		
Used to read:Appendix 4, GBR 830-201 Protocol Amendment 2.0 (contents reflecting protocol version 3 [amendment 2] changes were removed)	Now reads: Appendix 4, ~~GBR 830-201 Protocol Amendment 2.0~~**Summary of Changes in Current Protocol Amendment** (contents reflecting protocol version 4 [amendment 3] changes have been added)	Previous appendix 4 that described changes in protocol version 3 (amendment 2) has been removed. A new appendix 4 entitled "Summary of Changes in Current Protocol Amendment," which describes changes in current protocol version 4 (amendment 3), has been added. This change was done to remove an extra appendix that is no longer needed, avoid confusion at the site, and reduce the total number of pages in the protocol.