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

NCT02683928

Document Date: 12-Apr-2018

STATISTICAL ANALYSIS PLAN

Version 6.0: Addendum to Version 5.0

DATE OF PLAN:

12-Apr-2018

BASED ON:

Statistical Analysis Plan (SAP) Version 5.0, 06-Jul-2017

Protocol Amendment 3.0 Protocol Version 4.0, 16-Feb-2017

Case Report Form (CRF) Version 5.0, 03-June 2016

STUDY DRUG:

GBR 830

PROTOCOL NUMBER:

GBR 830-201

STUDY TITLE:

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

SPONSOR:

Glenmark Pharmaceuticals SA, Chemin de la Combeta 5, 2300 La Chaux-de-Fonds, Switzerland

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been reviewed and approved by:

Hui Fang

Project Statistician
Glenmark Pharmaceuticals

Signature

Apr. 12, 2018
Date

Gerhard Wolff

Vice President Clinical Sciences
Glenmark Pharmaceuticals

Signature

04/12/2018
Date

TABLE OF CONTENTS

1. REVISION HISTORY AND SUMMARY OF CHANGES

REVISION HISTORY

Statistical Analysis Plan (SAP) version 6.0, an SAP addendum, and SAP version 5.0 supersede the previous versions of the SAP.

Version	Description	Document Date
1.0	Draft, not signed-off	06-Sep-2016
2.0	Draft, not signed-off	18-Jan-2017
3.0	Draft, not signed-off	14-Mar-2017
4.0	Signed-off	04-Apr-2017
5.0	Signed-off	06-Jul-2017
6.0	Addendum to version 5.0	26-Mar-2018

SUMMARY OF CHANGES IN ADDENDUM V6.0

The following table and listings that were pre-specified in the protocol are being added to the SAP in addendum v6.0.

Table or Listing Number	Title	Analysis Set
Table 14.2.4.6	Percent Change from Baseline in Body Surface Area Involved for Atopic Dermatitis at Each Visit	Full Analysis Set
Listing 16.2.6.17	Body Surface Area Involved for Atopic Dermatitis	Full Analysis Set
Listing 16.2.6.18	Whole Body Photography	Full Analysis Set

2. PURPOSE OF ADDENDUM

The purpose of this statistical analysis plan (SAP) addendum is to add 1 summary table for body surface area (BSA), 1 listing for BSA, and 1 listing for whole body photography. These data were pre-specified in the protocol and were collected in the case report form (CRF) database prior to database lock.

The SAP version 5.0 dated 06-Jul-2017 was signed-off by Glenmark on 10-Jul-2017 and by Numerus (the Contract Research Organization that performed the statistical analysis) on 11-Jul-2017, before the database lock on 11-Jul-2017. In both study protocol version 4.0 and SAP version 5.0, percent improvement in BSA involved for atopic dermatitis (AD) from baseline at each visit was listed as one of the secondary efficacy endpoints for all subjects, and whole body photography was also to be collected for subjects who gave specific consent for the photography. However, there were no table or listing shell for BSA by visit and no listing shell for the whole body photography included in the SAP version 5.0.

These 3 outputs are needed for the clinical study report. The shells are provided in this statistical addendum. No statistical analyses will be performed for whole body photography.

APPENDIX 1. TABLE OF CONTENTS FOR DATA DISPLAY SPECIFICATIONS – ALL TABLES, LISTINGS AND FIGURES

Table, Listing or Figure Number	Title	Analysis Set
Table 14.2.4.6	Percent Change from Baseline in Body Surface Area Involved for Atopic Dermatitis at Each Visit	Full Analysis Set
Listing 16.2.6.17	Body Surface Area Involved for Atopic Dermatitis	Full Analysis Set
Listing 16.2.6.18	Whole Body Photography	Full Analysis Set

APPENDIX 2. DATA DISPLAY SPECIFICATIONS – NEW TABLE 14.2.4.6, NEW LISTINGS 16.2.6.17 AND 16.2.6.18

Table 14.2.4.6
Percent Change from Baseline in Body Surface Area Involved for Atopic Dermatitis at Each Visit
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (Day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 3 (Day 4)	N	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Percent change from Baseline to Visit 3 (Day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
etc.	Max.	xx	xx
Visit 14 LOCF	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Percent change from Baseline to Visit 14	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	Xx

Footnote: Visit 12 or Visit14 last observation carried forward (LOCF) was calculated as the last post baseline measurement prior to or on Visit 12 or Visit 14, respectively.

Listing 16.2.6.17
Body Surface Area Involved for Atopic Dermatitis
Full Analysis Set

Planned Treatment	Site ID-Subject ID	Visit (Study Day)*	Visit Date	BSA	Measurement Change from Baseline	Percent Change from Baseline
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	xx	N/A	N/A
		3 (4)	DDMMMYYYY	xx	xx	xx
		4 (8)	DDMMMYYYY	xx	xx	xx
		5 (15)	DDMMMYYYY	xx	xx	xx
		6 (22)	DDMMMYYYY	xx	xx	xx
		7 (29)	DDMMMYYYY	xx	xx	xx
		8 (32)	DDMMMYYYY	xx	xx	xx
		9 (36)	DDMMMYYYY	xx	xx	xx
		10 (43)	DDMMMYYYY	xx	xx	xx
		11 (50)	DDMMMYYYY	xx	xx	xx
		12 (57)	DDMMMYYYY	xx	xx	xx
		13 (71)	DDMMMYYYY	xx	xx	xx
		14 (85)	DDMMMYYYY	xx	xx	xx

Footnote: * indicates the baseline record; BSA = body surface area; N/A = not applicable.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.6.18
Whole Body Photography
Full Analysis Set

Planned Treatment	Site ID-Subject ID	Visit (Study Day)*	Visit Date	Subject Consent?	Photography Taken?	Results
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	xx	xx	xx
		3 (4)	DDMMMYYYY	xx	xx	xx
		4 (8)	DDMMMYYYY	xx	xx	xx
		5 (15)	DDMMMYYYY	xx	xx	xx
		6 (22)	DDMMMYYYY	xx	xx	xx
		7 (29)	DDMMMYYYY	xx	xx	xx
		8 (32)	DDMMMYYYY	xx	xx	xx
		9 (36)	DDMMMYYYY	xx	xx	xx
		10 (43)	DDMMMYYYY	xx	xx	xx
		11 (50)	DDMMMYYYY	xx	xx	xx
		12 (57)	DDMMMYYYY	xx	xx	xx
		13 (71)	DDMMMYYYY	xx	xx	xx
		14 (85)	DDMMMYYYY	xx	xx	xx

Footnote: * indicates the baseline record.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

STATISTICAL ANALYSIS PLAN PHASE IIA

VERSION: 5.0
DATE OF PLAN:

6-JUL-17

BASED ON:

Protocol Amendment 3.0 Protocol Version 4.0 16-Feb-2017

CRF Version 5.0 3-June 2016

STUDY DRUG:

GBR 830

PROTOCOL NUMBER:

GBR 830-201

STUDY TITLE:

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

SPONSOR:

Glenmark Pharmaceuticals SA

Chemin de la Combeta 5,

2300 La Chaux-de-Fonds,

Switzerland

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

Michelle Light

Senior Statistician
Numerus Ltd

Signature: MJLgl4 Date: 10 Jul 2017

Jonathan Alsop

Director
Numerus Ltd

Signature: Date: 11 Jul 2017

This document has been reviewed and accepted by:

Hui Fang

Project Statistician
Glenmark Pharmaceuticals SA

Signature: Date: Jul. 10, 2017

Vinu C A

Principal Scientist
Glenmark Pharmaceuticals SA

Signature: Date: 7th July. 2017

Gerhard Wolff

Vice President Clinical Sciences
Glenmark Pharmaceuticals SA

Signature: Date: 07/10/2017

TECHNICAL SUMMARY REPORT (TSR)

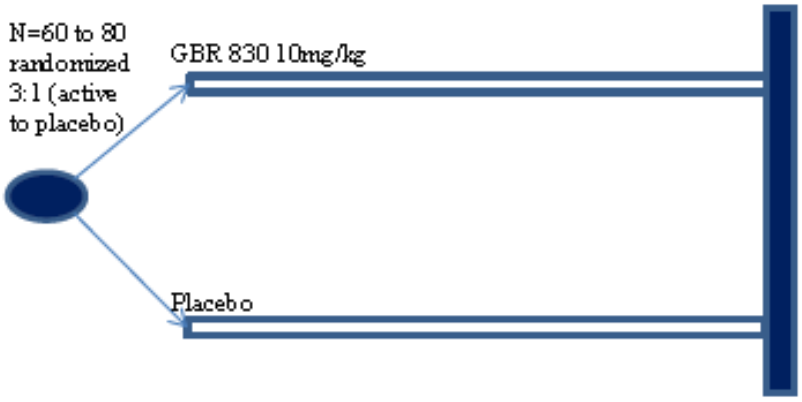
Name of Sponsor/Company Glenmark Pharmaceuticals SA	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: GBR 830	**Page:**	
Name of Active Ingredient: GBR 830		
Title Of Study: A Phase IIa, Double-Blind, Randomized, Placebo-controlled, Exploratory Study to Evaluate the Safety, Biological Activity and Pharmacokinetics of GBR 830 in Adult Subjects With Moderate-to-Severe Atopic Dermatitis		
Investigators: Study Center(s): Approximately 16 sites in regions that include USA and Canada.		
Studied period (years): approx. 2 years	**Phase of development:** Phase IIa	
Objectives: Primary: • Safety and tolerability of repeated doses of GBR 830 in adult subjects with atopic dermatitis (AD). • Effect of repeat doses of GBR 830 on biomarkers of disease activity in adult subjects with AD. Secondary: • Effect of GBR 830 on additional efficacy parameters in adult subjects with AD. • Pharmacokinetics (PK) of repeated doses of GBR 830 in adult subjects with AD. • Immunogenicity of GBR 830 in adult subjects with AD. Exploratory: • Additional exploratory objectives to understand the mechanism of GBR 830 including effect on cellular infiltrates and immune pathways.		

Methodology:

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 subjects 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.

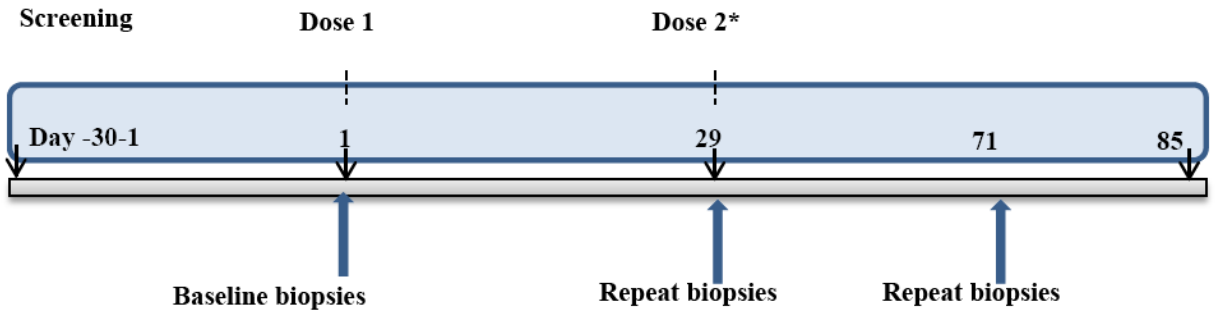
During the screening phase, after providing informed consent all subjects will be screened for eligibility prior to inclusion in the study and sufficient numbers of subjects will be screened to ensure at least 40 subjects meeting the eligibility criteria will be enrolled. At screening, subjects will be assessed on Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Severity Scoring of Atopic Dermatitis (SCORAD) and Body Surface Area (BSA) rating scales for AD. Subjects 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, subjects 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. . Subjects 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 subject will receive two doses of GBR 830 or placebo administered 4 weeks apart on Day 1 and Day 29. Subjects 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). Subjects will return for follow-up visits as mentioned in Appendix 1 - schedule of events. The study site will contact subjects by telephone approximately 24 hours after each infusion (Days 2 and 30) for concomitant medication and procedures, and a general adverse event (AE) query.

Figure 1: Study Design Schematic



Apart from the dosing visits, subjects will be seen in the clinic on Days 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.

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.

Number of Subjects (planned and analyzed):

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

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

Diagnosis and main criteria for inclusion (see protocol section 9):

The target study population is adult males and females with chronic moderate-to-severe AD as defined by EASI score of ≥ 12; SCORAD of ≥ 20; IGA score of ≥ 3 at baseline and with history of inadequate response to topical therapies.

Inclusion criteria:

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

1. Male or female subjects, 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 et al, 1980) 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).
4. Subject's body mass index (BMI) should be within the range 18.5-35 kg/m^2 (inclusive); weight must be ≥ 50 kg.
5. Subjects deemed fit to receive the study medication, as determined by medical history, vital signs, physical examinations, Electrocardiogram (ECG), laboratory studies, and other tests performed within 30 days prior to drug administration, as judged by the Investigator.
6. Subjects 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 patents should agree not to donate sperm until 180 days after administration of the last dose of the study medication. Female subjects should not donate eggs for 180 days following investigational product administration.

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

7. Female subjects of non-child-bearing-potential (i.e. are postmenopausal or permanently sterilized [bilateral oophorectomy, hysterectomy, bilateral salpingectomy]). Such subjects 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:

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

1. Subjects 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. Subjects 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°C (100.4°F) within one week of randomization.
4. Subjects who have evidence of active or latent tuberculosis as documented medical history, or test positive for QuantiFERON Gold Blood TB Test.
5. Subjects 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. Subjects 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. Subjects 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. Subjects 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. Subjects with a positive result from the drug and alcohol screen.
15. Subjects who test positive for disease markers of Human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C.
16. Subjects 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/prior to randomization (QTc calculated based on Fridericia's formula).
17. Subjects with lab values, which are significantly different from normal references ranges and/or judged clinical significant by the Investigator, including but not limited to:
    a) Subjects with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as determined by the modification of diet in renal diseases (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. Subjects 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 subjects unsuitable for study.
19. Subjects with a history of current or previous psychiatric illnesses or previous psychiatric events that would either put the subject 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.

Test product, dose and mode of administration:

GBR 830 (10 mg/kg) will be diluted in normal saline and administered as IV infusion over 60 minutes. Two doses will be administered at an interval of once every 4 weeks.

Duration of treatment: Screening phase (4 weeks), study duration including treatment phase and follow-up (12 weeks), total study duration for each subject (16 weeks). Screening phase occurs on days -30 to -1. Treatment phase occurs on day 1 and 29. Follow-up occurs on days 4, 8, 15, 22, 32, 36, 43, 50, 57, 71, and 85.
Reference therapy, dose and mode of administration: Placebo (formulation buffer) will be diluted in normal saline and administered as IV infusion over 60 minutes. Two doses will be administered at an interval of once every 4 weeks.

Criteria for evaluation (see protocol section 8):

Primary Endpoints:

. 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 AEs (SAEs), in adult subjects with moderate-to-severe AD.

. Effect of GBR 830 in adult subjects 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 Endpoints:

. Proportion of subjects who achieve an IGA score of 0 or 1 at each study visit.

. Proportion of subjects 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 numeric rating scale (NRS) and Dermatology Life Quality Index (DLQI) from baseline to each visit.

. Changes from baseline AD activity as determined by changes in Transepidermal water loss (TEWL).

. PK of GBR 830 in adult subjects with moderate to severe AD in terms of C_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, $t_{½}$, 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 Endpoints (change from baseline in levels of):

- 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, Dendritic cells) as assessed by CD3, FcEpsilon RI, and OX40L, OX40, and MBP.

. Serum total Immunoglobulin E (IgE), serum soluble OX40 (sOX40), serum soluble OX40 ligand (sOX40L), and circulating eosinophil counts.

Safety:

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

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. Subjects, 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. 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)

The primary endpoint will be absolute change from baseline in the active AD mRNA expression signature.

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 sections below.

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.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

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

Safety Analyses

Adverse events will be summarized by system organ class, preferred term and treatment group. Subjects 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 subjects above or below a pre-specified threshold for each test.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate amino transferase
AUC_{0-t}	Area under the curve (0 to t)
AUC_{0-tau}	Area under the curve (0 to tau)
$AUC_{0-\infty}$	Area under the curve (0 to infinity)
CCL	Chemokine ligand
CMH	Cochran Mantel-Haenszel
CV	Coefficient of variation
BLQ	Below the lower limit of quantification
BMI	Body mass index
BSA	Body surface area
C_{max}	Maximum observed serum concentration
CRO	Contract research organization
CSR	Clinical study report
DOB	Date of birth
DLQI	Dermatology Life Quality Index
DP	Drug product
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FSH	Follicle stimulating hormone
GCP	Good clinical practices

GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
HIV	Human immunodeficiency virus
ICD-9	International Classification of Diseases – 9th Edition
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IHC	Immunohistochemistry
IL	Interleukin
IRB	Institutional review board
IV	Intravenous
LOCF	Last observation carried forward
LS	Lesion skin
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MDRD	Modification of diet in renal disease
MMRM	Mixed model repeated measures
NLS	Non-lesion skin
PK	Pharmacokinetic
RO	Receptor occupancy
s.d.	Standard deviation
s.e.	Standard error
SAE	Serious adverse event
SAP	Statistical analysis plan
SCORAD	Severity Scoring of Atopic Dermatitis
$t_{½}$	Elimination half life
TARC	Thymus and activation-regulated chemokine
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
TEWL	Trans epidermal water loss
T_{regs}	Regulatory T cells
TS	Transdermal Delivery System-Placebo

ULN	Upper limit of normal
V	Visit
VAS	Visual Analogue Scale
WBC	White blood cell count
WHO (DDE)	World Health Organization (Drug Dictionary Enhanced)

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol GBR 830-201.

Protocol Revision Chronology:		
Protocol	12-OCT-2015	Original.
Amendment 1	19-MAY-2016	Amendment No. 01: The changes of this amendment were non-substantial.
Amendment 2	07-NOV-2016	Amendment No. 02: The changes of this amendment were substantial and are detailed in the protocol version 3.0.
Amendment 3	16-FEB-2017	Amendment No. 03: The changes of this amendment were substantial and non-substantial and are detailed in the protocol version 4.0.

This SAP was developed in accordance with ICH E9 guidelines. All decisions regarding final analysis, as defined in this SAP document, will be made prior to database freeze (unblinding) of the study data (unless otherwise stated).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary study objectives are as follows:

- Safety and tolerability of repeated doses of GBR 830 in adult subjects with atopic dermatitis (AD).
- Effect of repeated doses of GBR 830 on biomarkers of disease activity in adult subjects with AD.

3.1.2. Secondary Objective

The secondary study objectives are as follows:

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

3.1.3. Exploratory Objective

The exploratory study objective is as follows:

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

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoints of the study are as follows:

- 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 AEs (SAEs), in adult subjects with moderate-to-severe AD.
- Effect of GBR 830 in adult subjects 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.

3.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- Proportion of subjects who achieve an Investigator's Global Assessment (IGA) score of 0 or 1 at each study visit.
- Proportion of subjects who achieve an Eczema Area and Severity Index (EASI) 50 and 75 response at each study visit.
- Percent improvement in clinical scores EASI, Severity Scoring of Atopic Dermatitis (SCORAD), IGA, Body surface area (BSA), Pruritus numerical rating score (NRS) and Dermatology Life Quality Index (DLQI) from baseline to each visit.
- Changes from baseline AD activity as determined by changes in Transepidermal water loss (TEWL).
- PK of GBR 830 in adult subjects with moderate to severe AD in terms of C_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$, $t_{½}$, 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.

3.2.3. Exploratory endpoints

The exploratory endpoints of the study are as follows:

- Cytokines 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, OX40, MB, and OX40L.
- Serum total Immunoglobulin E (IgE), serum soluble OX40 (sOX40), serum soluble OX40 ligand (sOX40L), and circulating eosinophil counts.

4. STUDY DESIGN

4.1. Summary of 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 subjects 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 subjects will be screened for eligibility prior to inclusion in the study and sufficient number of subjects will be screened to ensure at least 40 subjects meeting the eligibility criteria will be enrolled. At screening, subjects will be assessed on EASI, IGA, SCORAD and BSA rating scales for AD. Subjects will be withdrawn from use of other medication being used to control their AD. On Day 1, prior to dosing, subjects 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 subjects will be randomized such that approximately 40 evaluable subjects complete at least the Day 29 visit. Approximately 60 to 80 subjects 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.

Subjects 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 subject will receive two doses of GBR 830 or placebo administered 4 weeks apart on Day 1 and Day 29. Subjects 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). Subjects will return for follow-up visit is as mentioned in Appendix 1 – schedule of events. The study site will contact subjects 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, subjects 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 subjects 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 subject in the study.

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

Figure 1: Study Design Schematic

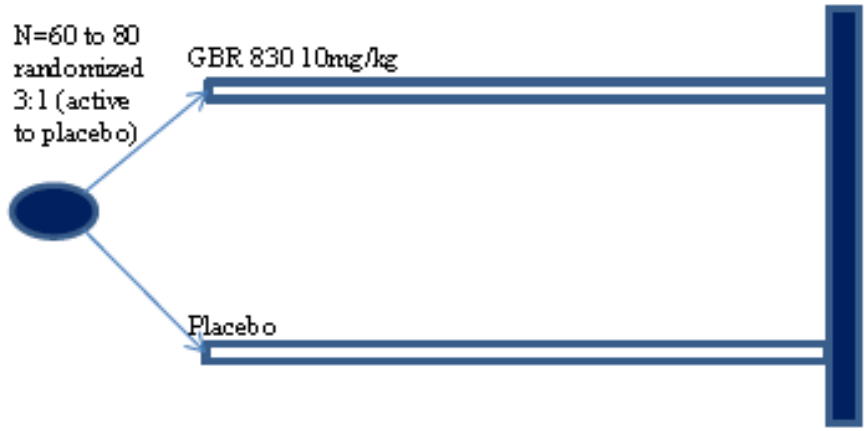
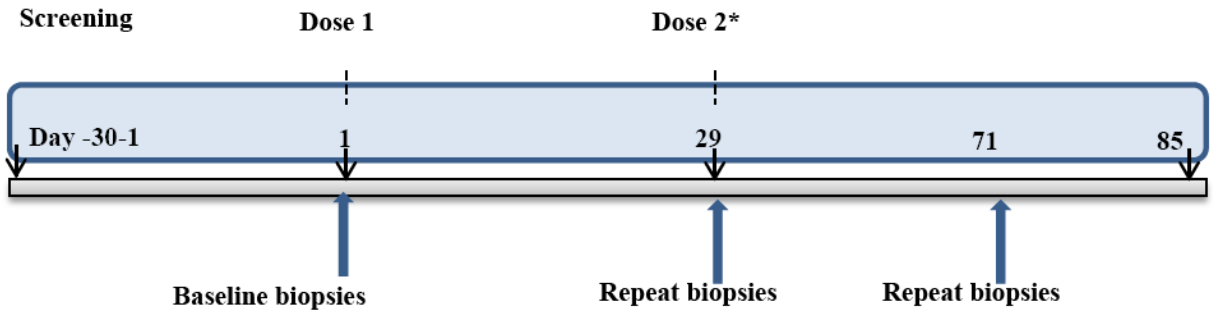


Figure 2: Study Flow Chart



*The timing of the 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.

4.2. Definition of Study Drugs

Investigational products:

Test drug: GBR 830 (10mg/kg) drug product (DP), diluted in normal saline and administered as IV infusion over 60 minutes. Two doses administered at an interval of once every 4 weeks.

Placebo: Formulation buffer, diluted in normal saline and administered as IV infusion over 60 minutes. Two doses administered at an interval of once every 4 weeks.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

No formal sample size calculations were performed for this study. The sample size chosen is based on experience from previous studies of similar nature. Subjects, 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 be replaced. The sample size of 40 adult subjects with AD randomized in ratio of 3:1 (GBR 830 versus placebo) is considered to be sufficient to provide description information on the PK, safety, tolerability and potential efficacy of GBR 830.

4.3.2. Sample Size Re-estimation

The sample size for this study has not been formally re-estimated. However, at the time of SAP writing the number of subjects randomized has been increased to 60 to 80 subjects, in order to allow for high levels of subject withdrawal and provide approximately 40 evaluable subjects.

4.4. Randomization

Following confirmation of eligibility, subjects were assigned a randomization number through interactive voice response system (IVRS)/interactive web response system (IWRS) central randomization. The randomization scheme and identification for each subject will be included in the final CSR for this study. The randomization list was generated using Statistical Analysis System (SAS) Version 9.1.3 or higher. All eligible subjects entering the study were randomized to one of the two treatment arms. If a subject discontinues from the study, the subject number will not be re-used and the subjects will not be allowed to re-enter the study.

Subjects are randomly assigned to receive either GBR 830 or placebo in a 3:1 ratio. A randomization number that uniquely identified each subject and the subject's treatment is assigned on Day 1. Randomization numbers are allocated from the schedule in strict chronological order.
A sufficient number of subjects (approximately 60 to 80) will be randomized such that approximately 40 evaluable subjects complete at least the Day 29 visit.

- For subjects 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 subjects randomized after protocol version 3 (amendment 2 who do not complete at least the Day 29 visit: Replacement of subjects (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.

4.5. Clinical Assessments

4.5.1. Efficacy Assessments

4.5.1.1. 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).

4.5.1.2. 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). 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 subject 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).

4.5.1.3. 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 subjects who achieve an IGA 0 or 1 score is another key secondary endpoint which will be included in the primary analysis.

4.5.1.4. NRS

Pruritus Numerical Rating Scale (NRS): Subjects 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?" Subject compliance on the pruritus NRS will be followed at each clinic visit.

4.5.1.5. DLQI

The Dermatological Life Quality Index (DLQI) is a simple, subject-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 "nor at all", "not relevant" responses score 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 et al, 1994).

4.5.2. Pharmacokinetic, Pharmacodynamic and Biomarker Assessments

4.5.2.1. 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.

The minute of collection of each blood sample will be recorded. Actual time points will be used for PK calculations.

The details of sample collection, processing and storage are outlined in the laboratory manual. The sample will be shipped to the specified bioanalytical laboratory. Serum concentration of GBR 830 will be quantified using a validated Enzyme-linked immunosorbent assay (ELISA) method.

4.5.2.2. Immunogenicity Assessments

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

4.5.2.3. Biomarker Assessments

4.5.2.3.1. 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 are outlined in the lab manual.

4.5.2.3.2. Cytokine and Chemokines

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

4.5.2.3.3. Total IgE

Subjects 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 are outlined in the lab manual. Blood samples will be collected at appropriate time points defined in Appendix 1.

4.5.2.3.4. Transepidermal Water Loss

Transepidermal Water Loss (TEWL) 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 is provided in the Study Reference Manual.

4.5.2.3.5. Immunohistochemistry (IHC)

Skin biopsy samples will be collected at appropriate time points defined in Appendix 1. Two punch biopsies (1 from lesion skin (LS) and 1 from non-lesion skin (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 are outlined in the lab manual.

4.5.2.3.6. 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.

4.5.2.3.7. Serum Soluable OX40 Ligand and Serum Soluable 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.

4.5.3. 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.

4.5.4. Schedule of Assessments

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

4.5.4.1. Visit Identification (ID)

The visits are defined at the following study days:

- Visit ID 1 (V1) [Baseline visit]: Study day -30 to -1
- V2: Study day 1
- V3: Study day 4 ± 1
- V4: Study day 8 ±1
- V5: Study day 15 ± 1

- V6: Study day 22 ± 2
- V7 (Dosing visit)*: Study day 29 ± 1
- V8: Study day 32 ± 1
- V9: Study day 36 ± 1
- V10: Study day 43 ± 1
- V11: Study day 50 ± 2
- V12: Study day 57 ± 2
- V13: Study day 71 ± 2
- V14: Study day 85 ± 2

*If the second dosing visit is altered, then the time-points for visits V12, V13 and V14 will be calculated from the second infusion.

4.5.4.2. Visit windows

The visit windows for assessments are defined as follows:

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 hrs (Day 71) ± 48 hrs, and 2016 hrs (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 hrs (Day 57) ± 48 hrs, 1680 hrs (Day 71) ± 48 hrs, and 2016 hrs (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 ECG recording:

- V2:
  - Pre-dose: before administration of each dose
  - Post-dose: 2 hrs ± 30 mins and 6 hrs ± 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: 2 hrs ± 15 mins and 3 hrs ± 15 mins estimated from the end time of infusion

V12, V13, V14: 1344 hrs (Day 57) ± 48 hrs, 1680 hrs (Day 71) ± 48 hrs, and 2016 hrs (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 hrs (Day 57) ± 48 hrs, 1680 hrs (Day 71) ± 48 hrs, and 2016 hrs (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 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 sample will be recorded.

5. PLANNED ANALYSES

5.1. Interim Analyses

There is no interim analysis planned.

5.2. Final Analyses

The final analysis top line results will be performed two weeks after the receipt of post-database lock data. All other analysis will be performed four weeks after the receipt of post-database lock data.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will include a "footer" providing explanatory notes that indicate:

- Date of data extraction (this is to link the output to the archived database that is locked to ensure the replication of the results.)
- Date of output generation.
- SAS program name, including the path that generates the output.
- Other output specific details such as abbreviation and acronym definitions, relevant methodological detail.

Tables will include reference(s) to the subject data listing(s) that supports the summary data.

The tables will be organized with respect to treatment group (GBR 830 then placebo) and a column will be included to summarize all treated subjects. Row entries in tables will only appear if data exists for at least one subject (e.g., a row with all zeros will not appear). The exception to this rule applies to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Summary tables for medications and medical conditions are coded according to the WHO DDE September 2015 dictionary. Adverse event preferred terms and body/organ systems are coded using MedDRA 19.0 March 2016 dictionary. The MedDRA dictionary will also be used in the coding of signs and symptoms, medical history, physical examination abnormalities, and clinical diagnoses.

Supportive subject data listings will be sorted and presented by treatment group (group). Listings also include subject number, visit number, visit date, and days relative to the initiation of double-blind treatment.

No imputations are imposed for missing clinical data apart from for the primary and secondary endpoints analysis. Imputed or derived data will be flagged in the subject listings. Imputed data are not incorporated into any raw or primary datasets. These data are retained in derived analysis datasets.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The tables and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ).

The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post text tables usually occupy Appendix 14 and the individual subject data listings are put in Appendix 16. All post text tables will have a main number level 14 and listings 16. The subject accounting and disposition table are usually first in the first section of the report therefore will be numbered Table 14.1. The supportive subject data listing would be Listing 16.1.

The title will be complete, accurate, and concise. The last line of the title will provide the analysis group being summarized (e.g., Full Analysis Set, Safety Analysis Set, Biological Activity Set or Pharmacokinetic Analysis Set). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Standing Blood Pressure (mmHg) and Heart Rate (bpm)." Whether in the title or body of a table or listing, units must always be specified for all appropriate data.

If possible, variables being summarized and statistics reported should appear in the left most column of a table. The next columns for treatment groups should report the data from left to right for GBR 830, placebo and (optional) overall subjects, respectively.

In general, the listings will be sorted and presented by treatment assignment, and subject number. From left to right, the treatment assignment, subject number, visit number, visit date, and relative day should appear. All tables and listings will have explanatory notes that give, data extraction date, output generation date, and complete program name and path where it is stored. The definition of all derived variables and decodes for coded data will appear in the notes. Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.

6.3. Data Management

Data from the study will be managed by Glenmark Pharmaceutics Ltd or their representative.

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, Institutional Review Board [IRB]/Independent Ethics Committee [IEC] approvals) and pertinent hospital or clinical 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 subject's source documents.

All data verification, using hospital or clinic records, will be performed respecting subject 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 subject 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 there is complete and accurate.

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

Derived datasets are created using (SAS®) software. Data analyses and summary tables are generated using SAS version 9.4 or above.

6.4. Data Presentation Conventions

Continuous variables (e.g. age) will be summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), median and minimum and maximum). Categorical variables (e.g. race) will be summarized using counts and percentages. Percentages are calculated using the total subjects per treatment group.

The following conventions are applied to all data presentations and summaries.

For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.

For categorical variables, the number and percentage of responses are presented in the form “XX (XXX)” where the percentage is in the parentheses.

Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.

Wherever possible, data will be decimal aligned.

P-values will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

All tables and listings will use Times New Roman font of size 9. Page layout will be landscape and page size A4 unless otherwise specified in the shells.

The table and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a

deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

6.5. Analysis Populations

Prior to hard database lock, a final blinded data review meeting to verify the data that will be used for analysis set classification. The Pharmacokinetic Analysis Set will be assessed and finalized once data has been unblinded post database lock.

6.5.1. Screen Failures

Subjects who give informed written consent but are not dispensed study treatment are considered screen failures. No attempt will be made to further characterize the reason for screen failures (e.g., lost-to-follow-up, did not meet entry criteria, administrative) in summary tables due to the paucity of information usually gathered however the verbatim reason for screen failure will be included in the supportive listing.

6.5.2. Full Analysis Set (FAS) Population

The Full Analysis Set (FAS) will consist of all subjects who are randomized and have received at least one partial or full dose of study treatment. FAS population will be used for the analysis of the efficacy data not obtained from skin biopsy. Subjects will be analyzed according to the treatment by which they were randomized to.

6.5.3. Biological Activity Set (BAS) Population

The Biological Activity Set (BAS) will consist of all FAS subjects who have at least one post-baseline skin biopsy (Visit 7, Visit 13), and received two doses of study drug. The primary analyses on biomarkers of disease activity obtained from biopsy will be based on the BAS. Subjects will be analyzed according to the treatment by which they were randomized to.

6.5.4. Safety Analysis Set (SAF) Population

The Safety Analysis Set (SAF) consists of all subjects who took at least one full or partial dose of study treatment and will be used in the assessment and reporting of safety data. Subjects will be analyzed according to the treatment which they received rather than the treatment which they were randomized to. If a subject receives both treatments over the course of the study, they will be assigned to the active drug.

6.5.5. Pharmacokinetic Analysis Set (PKAS) Population

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the Safety Analysis Set population for which sufficient serum concentration data is available to:

1. facilitate derivation of at least one PK parameter, and
2. the time (HH:MM) of dosing on the day of sampling is known

for at least one of the dosing visits. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. The PKAS will include only subjects treated with GBR830. The exclusion of subjects or time-points from the PKAS are defined as:

- Subjects will be excluded from the analysis if the pre-dose concentration level before 1st dosing event is greater than 5% of the individual subject C_{max} after 1st dose.
- Subjects will be excluded if all of their post-dose values are less than lower limit of concentration.
- Subjects will be excluded if there is a major protocol deviation likely to affect the validity of the concentration levels.

6.6. Baseline Definition

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (years) = FLOOR((date of informed consent – date of birth)/365.25) where FLOOR( ) function returns the integer part of the result.

6.7.2. Age at AD diagnosis

Subject's age in years at AD diagnosis will be calculated based on date of AD diagnosis using the following formula:

Age at AD diagnosis (years) = FLOOR((date of AD diagnosis – date of birth)/365.25)

Where FLOOR() function returns the integer part of the result.

6.7.3. Study Day

If the date of interest occurs on or after the first infusion/randomization date then study day will be calculated as (date of interest – date of first infusion/randomization) + 1 day. If the date of interest occurs prior to the first infusion/randomization date then study day will be calculated as (date of interest – date of first infusion/randomization). There is no study day 0.

6.7.4. Change from Baseline

Baseline is defined as study day 1 unless stated otherwise.

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as [(change from baseline/baseline result) x 100].

If either the baseline or the post-baseline result is missing, the change from baseline and percentage change from baseline is set to missing as well unless imputation rules are applied for efficacy endpoints.

6.7.5. Visit 12 and Visit 14 LOCF Visits

The Visit 12 and 14 LOCF derived visits are defined on a Last Observation Carried Forward basis as the last measurement available for each subject up to or on Visit 12 and 14. These visits will be used for the analysis of secondary endpoints (EASI, IGA, SCORAD, DLQI, TEWL).

For subjects who discontinue the study early and have completed the Visit 14/EOS assessment their Visit 12 and 14 LOCF will be derived using the re-mapped visit specified in 6.7.6

6.7.6. End of Study Visit

Unless otherwise specified, the end of study visit will include those subjects who complete Visit 14 or who complete the early withdrawal visit. It will be abbreviated to Visit 14/EOS.

For the analysis of secondary efficacy variables (EASI, IGA, SCORAD, DLQI, TEWL), for patients who withdraw prematurely from the study and complete the Early Termination Visit, their Visit 14/EOS visit will be re-categorized as the visit immediately following their last scheduled visit.

6.7.7. Multiple Assessments

Where multiple assessments occur within the same visit, the visit closest to the scheduled visit day described in the protocol will be used. If the values are equidistant to the scheduled visit day, the mean of these values is used for the summaries over time (by visit) in the case of continuous data, and the maximum of these values in the case of ordered categorical data. If the data is categorical, e.g. normal/abnormal not clinically significant/abnormal clinically significant then the assessment with the worst case scenario will be selected.

6.7.8. Missing Efficacy Endpoints

Data will be assumed to be missing at random (MAR). Subjects that dropout are assumed will behave similarly to other subjects in the same treatment group, and with similar covariate values, had they not dropped out.

Missing data will be imputed where necessary and details can be found in Section 8.

6.7.9. Missing Start and Stop Dates for Prior and Concomitant Medication

Incomplete concomitant medication start and/or stop dates will be imputed as follows:

- If either the start of medication date is completely missing or the month and/or year of the start date is missing, the start date will be set to the treatment start date. If imputed start date is after the stop date, then change the imputed start date to stop date minus 1 day.
- If only the day is missing, the day will be set to the first day of the month except if the start month is the same as the treatment start month. If the latter is true, the start day will be set to the treatment start day. If imputed start date is after the stop date, then change the imputed start date to stop date minus 1 day.
- No imputations will be applied to the stop date.

Imputed dates will be flagged in the subject data listings.

6.7.10. Missing Start and Stop Dates for Adverse Events

Completely missing or partially missing AE start dates will be imputed as follows:

- If the AE start date is completely missing or the month and/or year are missing, the AE start date will be set to the treatment start date. If imputed start date is after the stop date, then change the imputed start date to stop date minus 1 day.
- If only the day is missing, and month and year are the same as treatment start date then start date will be set to the treatment start date. Otherwise the first day of the month will be assumed. If imputed start date is after the stop date, then change the imputed start date to stop date minus 1 day.
- No imputations will be applied to the stop date.

Imputed dates will be flagged in the subject data listings.

7. STUDY POPULATION

The study population will be analyzed using the Full Analysis Set unless otherwise specified.

7.1. Subjects Disposition

Subject disposition will be summarized using counts and percentages. Percentages will be based on the number of randomized subjects. All subjects screened and randomized will be summarized and listed.

The count and percentage of subjects included in each analysis set (as described in Section 6.5) will be presented. Percentages will be based on the number of randomized subjects.

The count and percentage of subjects who completed or discontinued from the clinical study will be summarized in a table and listed by treatment arm and overall. Percentages will be based on the number of randomized subjects. This will include a summary of the reasons for early termination or withdrawal from the study.

The following categories for early termination and withdrawal from the study will be presented:

- Withdrawal of consent
- Adverse event
- Investigator's discretion
- Non compliance with study procedures/protocol deviation
- Pregnancy
- Subjects requiring rescue medications or interventions/treatment with another therapeutic agent
- Disease progression/exacerbation
- Subjects randomized in the study who withdrawal their consent for the first post-baseline skin biopsies
- Lost to follow-up
- Death
- Other

For subjects who are non-completers a listing will be provided containing further details on the reasons for early termination/withdrawal and the Study Day of early termination/withdrawal see section 6.7.3 for Study Day calculation.

Descriptive statistics will be provided for the subject's time on study and will be analyzed using the Full Analysis Set. Time on study (days) will be calculated as:

End of Study Date – Randomization Date + 1 day

A subject listing will be provided containing, for each subject, the date of first and last use of study treatment and the date of withdrawal from study.

7.2. Screen Failures

Screen failures are subjects who are screened but not randomized. The number of subjects who are screening failures will be summarized.

A subject listing will be provided on all screen failures including the reason for screening failure. Screen failure subjects will neither contribute to other data presentations, nor participate in formal analyses.

7.3. Protocol Deviations

A subject listing will be provided containing detail of the protocol deviation as captured in the CRF, including the protocol deviation number, date reported, deviation coding, protocol deviation reportable to ethics (yes or no) and also any further detail; for example a description of the actions taken (if any).

The protocol deviation coded terms are defined as follows:

- Subject non-compliance with study procedures
- Missed dose(s)
- Extra dose(s)
- Fasting period not respected
- Randomization error
- Study visit not done
- Visit performed out of window
- Procedure(s) done but not required by the protocol
- Prohibited Medication
- Study procedure(s) not done
- Time window / order of events for study procedures not respected
- Washout period not respected
- Other

7.4. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize baseline demographics and characteristics separately for subjects in each analysis set (FAS, BAS and PKAS).

Descriptive statistics will be provided for the following continuous variables:

- Age (years) at entry into the study
- Age (years) at AD diagnosis
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) [This will be calculated in the clinical database from baseline height and weight.]
- Body Surface Area (m^2) [This will be calculated using BSA = 0.007184 x weight $(kg)^{0.425}$ x height$(cm)^{0.725}$ (Du Bois D, Du Bois EF, 1916).]

The following categorical demographics will be summarized using count and percentages of subjects by treatment group and overall. Percentages will be based on the appropriate analysis set:

- Age group at study entry
  - < 65 years
  - >= 65 years
- Sex
  - Male
  - Female
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
- Race
  - American Indian or Alaska Native
  - Asian
  - Black
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other

- Country
  - USA
  - Canada
- Child bearing potential (female only)
  - Yes
  - No
    - Post menopausal
    - Permanently sterilized
    - Duration of non child bearing potential (≤1 year, > 1 year)

Child bearing potential will be summarized for females only and percentages will be calculated using female subjects only. All demographics will be presented in a subject listing.

7.5. Listing of Subject Inclusion and Exclusion Criteria

A listing will be provided for all screened subjects which states for each subject whether the inclusion and exclusion criteria were met and, if not met, the applicable failed inclusion/exclusion criteria reason as captured in the CRF. The enrollment status (randomized or screen failure) and if randomized, the treatment allocated will also be listed.

7.6. Medical History and Medical Conditions Present at Entry

Medical history at baseline will be summarized in three separate tables for the Full Analysis Set by treatment group and overall:

- AD history
- Medical/surgical history
- Smoking, alcohol and drug abuse history

For AD history the following continuous variables will be summarized using descriptive statistics:

- Time since AD diagnosis (years)

The following categorical variables will be summarized using counts and percentages. Percentages will be based on the analysis set:

- Time since AD diagnosis category

  - < 2 years
  - 2 – 5 years
  - >= 5 years
- Type of AD: Intrinsic; Extrinsic
- Any history of allergy: Yes; No
- Was patch test performed: Yes; No
- Any other concomitant atopic illness? Yes; No
  - Type of Concomitant atopic illness: Asthma; Allergic rhinitis, Skin conditions; Other
- Was Skin biopsy performed in past? Yes; No
  - Result of skin biopsy: Eosinophilic; Non-eosinophilic; Other
- Any treatment administered for AD or associated conditions? Yes; No

A subject listing will also be provided for AD history data.

Medical/surgical history will be considered as they are captured in the CRF.

Each preferred term within a body system will be summarized using counts and percentage. Percentages will be based on the analysis set. Subjects will be counted only once at the system organ class level and will be counted once for each applicable preferred term. Data will be sorted by descending frequency of system organ class, then descending frequency of preferred term within organ class for the overall group. The following body systems will be considered:

- HEENT
- Cardiovascular System
- Respiratory System
- Musculoskeletal System
- Dermatological System
- Skin and its appendages
- Lymphatic System
- Gastrointestinal System
- Genitourinary System
- Nervous System
- Endocrine System
- Immunological System

- Allergic Conditions
- Other

A subject listing of all medical/surgical history data will be provided including body system, preferred term, start and end dates, ongoing status and severity grade (mild; moderate; severe; not known).

Smoking, alcohol and drug abuse history will be summarized.

The following continuous variables will be summarized using descriptive statistics, for current users only (subjects with zero will be considered missing):

- Alcohol consumption, ml/week
- Number of cigarettes per day

The following categorical variables will be summarized using counts and percentages. Percentages will be based on the analysis set:

- Former/current alcohol user: Former; Current; N/A
  - History of alcohol abuse: Yes; No
- Former/current drug user: Former; Current; N/A
  - Does the subject meet DSM-V criteria for addiction or abuse: Yes; No
- Former/current smoker: Former; Current; N/A
- Former/current smokeless tobacco user: Former; Current; N/A

Missing data will also be summarized where appropriate.

A subject listing of smoking, alcohol and drug abuse history will also be provided. In addition to the above, it will include specified forms of drug and tobacco as well as stop dates for former users.

7.7. Prior Medication History

Medications with a start date before the date of the first dose of study treatment will be classified as a prior medication.

All prior medications will be coded by anatomic-therapeutic-class (ATC) coding system, WHO DDE (September 2015) and the data will be summarized by each ATC level and preferred term (generic name).

The Full Analysis Set will be used.

7.7.1. Diagnosis Related Medication History

Medications administered for AD and related conditions will be summarized using counts and percentages by preferred term for each treatment group and overall. Data will be sorted by descending frequency within the overall group.

A subject listing will be provided including medication start and stop dates, whether the medication is ongoing, dose, frequency of administration, route of administration, trade name (if known) and indication for use.

7.7.2. Non-Diagnosis Related Medication History

Those medications which are not considered in Section 7.7.1 will be summarized using counts and percentages by preferred term for each treatment group and overall. Data will be sorted by descending frequency within the overall group.

A subject listing will be provided including medication start and stop dates, whether the medication is ongoing, dose, frequency of administration, route of administration, trade name (if known) and indication for use.

7.8. Baseline Physical Examination

The results of the baseline physical examination will be listed by treatment group and subject. The following body systems will be listed:

- General appearance
- Neck
- HEENT
- Cardiovascular system
- Respiratory system
- Musculoskeletal system
- Skin
- Gastrointestinal System

- Genitourinary System
- Neurological System
- Other

Each body system will be categorized into one of the following: normal; abnormal, not clinically significant; abnormal, clinically significant.

The count and percentage of subjects whose physical examination is performed/not performed will be summarized.

7.9. Baseline Vital Signs

Baseline vital signs are defined as the vital signs measured at the visit immediately prior to the first dose of study drug.

Descriptive statistics will be used to summarize baseline vital signs by treatment group, for Safety Analysis Set subjects.

Descriptive statistics will be provided for the following vital signs:

- Systolic blood pressure (mmHg)*
- Diastolic blood pressure (mmHg)*
- Body temperature (°C)
- Pulse rate (beats per minute [bpm])*
- Weight (kg)
- BMI (kg/m^2)
- Body Surface Area (m^2)

*Blood pressure and pulse rate are tested in supine position.

Blood pressure, body temperature and pulse rate will be categorized as normal; abnormal, not clinically significant; abnormal, clinically significant and the count and percentage of subjects by treatment group will be summarized.

All baseline vital signs data will be displayed in subject listings and clinically significant findings will be flagged.

7.10. Baseline Laboratory Data

Baseline laboratory results are defined as the last assessment prior to the first dose of study treatment regardless of whether it was scheduled, retest or unscheduled. Since laboratory retests can occur for individual parameters, it is necessary to define the baseline individually for each parameter.

All laboratory tables will be analyzed using the Safety Analysis Set.

Summary tables will be presented for each category of data (Haematology, Serum Biochemistry, Liver Function Tests, Renal Function Tests, Lipid Profile, Urinalysis, Serology, Other [for full list of laboratory parameters see Section 9.4]) by treatment group and overall. Descriptive statistics will be used to summarize the data:

- Quantitative laboratory test result will include mean, median, standard deviation, minimum and maximum.
- Qualitative tests (e.g. some urinalysis assessments and serum Beta-HCG pregnancy test) will be categorized accordingly.

The results of the serum pregnancy test will be reported as positive or negative for the female subjects and not applicable (NA) for male subjects in the summary of hematology results. The set of laboratory parameters included in each table will correspond to those requested in the study protocol. Units will be as found in the data.

All baseline laboratory data will be listed and will include the type of visit (e.g. scheduled test, retest, or unscheduled), age, sex, laboratory test, test units, laboratory test result, and the laboratory standard normal ranges adjusted as appropriate for age and sex, if available.

7.11. Baseline ECG

Baseline ECG results are defined as the ECG results measured at the visit immediately prior to the first dose of study drug.

Descriptive statistics will be used to summarize baseline ECG results by treatment group and overall for Safety Analysis Set subjects.

Descriptive statistics will be provided for the following ECG results:

- Heart Rate (bpm)
- PR Interval (ms)
- RR Interval (ms)
- QRS Interval (ms)

- QT Interval (ms)
- QTcF Interval (ms)

The result of the ECG assessment will be categorized as normal; abnormal, not clinically significant; abnormal, clinically significant and the count and percentage of subjects by treatment group and overall will be summarized. Percentages will be based on the analysis set.

All ECG data will be displayed in a subject listing and clinically significant findings will be flagged. Triplicate ECG performed at baseline will be listed only.

7.12. Baseline Clinical Scores

Baseline clinical scores are defined as the clinical scores recorded at the visit immediately prior to the first dose of study drug. Descriptive statistics will be used to summarize baseline clinical scores by treatment group and overall.

Descriptive statistics will be provided for the following clinical scores:

- EASI
- SCORAD
- Pruritus NRS
- DLQI

The result of the IGA assessment will be categorized as not done; clear; almost clear; mild; moderate; severe/very severe and the count and percentage of subjects by treatment group and overall will be summarized. Percentages will be based on the Full Analysis Set.

7.13. Baseline Skin Biopsy (Non-lesion only)

The non-lesion samples will be collected at baseline only. The mRNA expressions and pathologic epidermal phenotype markers (referred to here after as biomarkers) will be log transformed and summarized for the Biological Activity Set. Descriptive statistics will be used to summarize the biomarkers by treatment group and overall.

19 biomarkers from RT-PCR Panels (normalized to hARP) and the Immunohistochemistry (IHC) and will be summarized. A selection of these markers is found in Section 8.6.1

8. EFFICACY

8.1. General Considerations

Categorical data will be summarized using counts and percentages.

Continuous data will be summarized using counts, mean, s.d., s.e., median, minimum, maximum and 25th and 75th percentile where appropriate.

Formal statistical tests will be two-sided using a significance level of 5%, unless stated otherwise.

The Full Analysis Set will be used for the analysis of efficacy data, except the biopsy data which will be analyzed using the Biological Activity Set.

8.2. Testing Statistical Assumptions Including Comparability at Baseline

There will be no tests performed on the baseline data.

8.3. Statement of the Null and Alternate Hypotheses

The primary objective of this study is safety therefore there are no null or alternative hypotheses stated in the protocol.

8.4. Subgroup Analyses

There are no planned subgroup analyses.

8.5. Multiple Comparisons and Multiplicity

There will be no adjustment for multiplicity in this study.

8.6. Analysis of the Primary Efficacy Endpoint

8.6.1. Primary Efficacy Analysis

The primary analysis will examine the effect of GBR 830 in adult subjects with AD in terms of change from baseline in selected biomarkers obtained from skin biopsies. Only the lesion samples will be analyzed for the primary efficacy analysis.

19 mRNA biomarkers (K16, IL13, IL17A, IL22, INFg, IL-23p19, IL-23p40, OX40L, MMP12, S100A12, IL-5, CCL17, CCL18, CCL11, CCL26, S100A9, CXCL10, FOXP3, TSLPR) from the RT-PCR Panels will be assessed for the primary endpoint analysis.

The 19 biomarkers will be normalized to housekeeping gene hARP and log transformed for analysis. Measurements under the limit of detections will be imputed as 20% of the minimum value observed for that biomarker normalized to hARP prior to the log transformation.

For each of the mRNA normalized to hARP, a mixed model repeated measure (MMRM) approach of the repeated measures data will be implemented. The outcome for each MMRM will be the changes from baseline in the log transformed biomarkers.

The model will include the following:

- Categorical fixed effects: planned study treatment, planned visit
- Continuous fixed effects: baseline (log transformed) biomarker
- Random effects: planned visits within subjects

An unstructured covariance structure will be used to model the within-subject variability. If this analysis fails to converge, no other structures will be fitted and only summary statistics will be provided for that biomarker.

From the model the geometric mean change (with 95% CIs) from baseline at Visit 13 will be obtained for each treatment group. The overall least squares mean treatment difference (with 95% CIs) and the p-value between GBR 830 and placebo will also be presented.

As there are no adjustments for multiplicity, no inferences will be drawn from the p-values of the mixed model.

The mRNA normalized to hARP will be summarized at baseline, each study visit (Visit 7, Visit 13) and for change from baseline by treatment group using descriptive statistics. The geometric mean (with 95% CI) and CV (%) will also be reported. If non-lesion samples are available these will also be summarized

Box plots by treatment will also be produced for each of the biomarkers.

Pathologic epidermal phenotype measures for H&E thickness, K16.IHC and Histological response will be summarized by visits at both baseline and post-baseline. In addition, CD3, Ki67, FcEpsilonRI, OX40, OX40L, MBP will also be summarized by visit for epidermis and dermis measures. If non-lesion samples are available these will also be summarized

8.6.2. Sensitivity Analyses of the Primary Efficacy Endpoint

Not required.

8.7. Analysis of the Secondary Endpoints

8.7.1. Proportion of subjects who achieve an IGA score of 0 or 1 at each study visit

IGA scores will be categorized as follows:

- 0 (clear) or 1 (almost clear)
- 2+ (mild, moderate, severe/very severe)

The proportion of subjects, who achieved the IGA scores above at each study visit (Visit 3 to Visit 14) and the Visit 12/14 LOCF visits, will be summarized by treatment group and overall.

For subjects who use prohibited medication, any IGA score on or after the date of first use of prohibited medication will be set to missing.

A Cochran-Mantel-Haenszel (CMH) test will be performed to compare the IGA categories above for GBR 830 treatment and placebo at both the Visit 12 LOCF and Visit 14 LOCF visits. The CMH test will be stratified by categorical baseline IGA score (less or equal to 3, greater or equal to 4).

8.7.2. Proportion of subjects who achieve an EASI 50 and 75 responses at each study visit

The proportion of subjects who achieve an EASI 50 (and 75) response each study visit (Visit 3 to Visit 14), the Visit 12/14 LOCF visits, will be summarized by treatment group and overall.

- An EASI 50 responder is defined as a subject with at least a 50% reduction in EASI score compared to baseline.
- An EASI 75 responder is defined as a subject with at least a 75% reduction in EASI score compared to baseline.

For subjects who use prohibited medication, any EASI score on or after the date of first use of prohibited medication will be set to missing.

A line plot will be produced of the EASI 50 rate over time by treatment group. Mean and SE (±1) will be presented.

8.7.3. Analysis of covariance EASI scores

For the Visit 12 LOCF change from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment and baseline EASI score as linear covariates.

The LS-means at Visit 12 LOCF for each treatment group will be provided as well as the treatment difference at Visit 12 LOCF, with the corresponding standard errors, associated 95% confidence intervals and p-value. If the assumptions of the ANCOVA are not met (e.g. not meeting any of the following: normality, homogeneity of variance, random independent samples or a linear relationship between the dependent variable and the covariates) then a non-parametric rank-based ANCOVA method will be used instead, where the ranked values are the change from baseline in EASI scores.

8.7.4. Percent improvement in clinical scores EASI, SCORAD, IGA, Pruritus NRS and DLQI from baseline to each visit

The percent change from baseline in the following clinical scores will be summarized by each treatment group at each study visit (Visit 3 to Visit 14), and for the Visit 12/14 LOCF visits

- EASI
- SCORAD
- IGA
- Pruritus NRS
- DLQI

For subjects who use prohibited medication, any clinical score on or after the date of first use of prohibited medication will be set to missing.

Line plots will be produced of the percentage change over time for Pruritus NRS and EASI score by treatment group. Mean and SE (±1) will be presented.

8.7.5. Changes from baseline AD activity as determined by changes in Transepidermal water loss (TEWL)

Lesion and non-lesion areas average transepidermal water loss (TEWL) reading values and change from baseline will be summarized separately at each planned study visit and the Visit 12/14 LOCF visits, as well as the change from baseline at each time point by treatment group and overall using descriptive statistics.

For subjects who use prohibited medication, the TEWL average reading on or after the date of first use of prohibited medication will be set to missing.

8.7.6. Anti-drug antibodies (ADA) to GBR 830 to evaluate immunogenicity.

Anti-drug antibodies (ADA) will be summarized using counts and percentages by treatment group at each planned study visit and overall (including the overall number of subjects and percentage of subjects with positive and negative ADA at any post baseline visit), for the following categories:

- Positive
- Negative
- Not done

The individual subject ADA results will be listed.

The impact of ADA on the PK will be evaluated graphically by scatter plot with individual subject concentration levels vs ADA status, stratified by treatment.

8.8. Analysis of the Exploratory Endpoints

All exploratory endpoints will be summarized using descriptive statistics as well as the geometric mean (with 95% CI) and CV (%).

The endpoints below will be analyzed as described below, however these analyses, and biomarkers, could be subject to change when the final exploratory biomarkers are known.

8.8.1. Change from Baseline in Cytokines in serum

The exploratory cytokines analysis will be determined after database lock of the study, therefore no statistical analysis of those parameters will be included in this SAP.

8.8.2. Change from Baseline in Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells)

Descriptive statistics will be summarized for each Leukocyte sub-population cell counts (Total T, T helper, Cytotoxic T, T_{regs}, Memory T cells) by treatment group , separately for baseline and each visit (Visit 7, Visit 13).

The actual and percentage change from baseline will also summarized by treatment group.

8.8.3. Change from Baseline in Cellular infiltrates (T-cells, dendritic cells) as assessed by CD3, FcEpsilon RI, OX40L, OX40 and MBP

Descriptive statistics will be summarized for Cellular infiltrates (T-cells, Dendritic cells) as assessed by CD3, FcEpsilon RI, OX40L, OX40 and MBP by treatment group and overall for baseline and each visit (Visit 7, Visit 13).

The actual and percentage change from baseline will also summarized by treatment group.

8.8.4. Change from Baseline in Serum total Immunoglobulin E (IgE), serum soluble OX40 (sOX40), serum soluble OX40 ligand (sOX40L) and circulating eosinophil counts.

Descriptive statistics will be summarized for total IgE, serum soluble OX40 (sOX40), serum soluble OX40 ligand (sOX40L), and circulating eosinophil counts by treatment group and overall for baseline and each visit (Visit 7, Visit 13).

The actual and percentage change from baseline will also summarized by treatment group.

8.9. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

If subjects use prohibited medication, and the deviation is classified as a major deviation by the medical monitor at the blinded review meeting, any clinical endpoint data (i.e. IGA, EASI, SCORAD, Pruritus NRS, DLQI, TEWL) collected on or after the recorded deviation will be considered as non-evaluable and set to missing.

The date of prohibited medications which will be used is the earliest reported date of a major deviation for each subject from the protocol deviations page of the CRF. Note that this date may be on or after the actual start date of the prohibited medication(s).

Descriptive statistics will be used to summarize the major deviations by study visit on which the first major deviation of prohibited medication occurs. Counts and percentages will be used to summarize the visits which have been excluded due to use of prohibited medication.

The assessment of major or minor deviation for prohibited medications be provided as a SAS dataset and incorporated into the analysis.

9. SAFETY AND TOLERABILITY

All safety analysis will be based on the Safety Analysis Set.

9.1. Treatment Emergent Adverse Event Preferred Term and Body/Organ System Summary Tables

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 subjects with moderate-to-severe AD will be assessed.
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 (March 2016).

Rules for missing AE dates are found in Section 6.7.10.

The analysis described below will be summarized for events considered to be treatment emergent. For an event to be treatment emergent it must have an onset date or worsening on or after the first dose of study drug. All AEs will be listed.

9.1.1. Summaries of Adverse Event Incidence Rates for All Subjects

The count and percentage of subjects with each of the following will be summarised by system organ class, preferred term and treatment group:

- AEs
- SAEs
- AEs leading to permanent withdrawal of study treatment
- AEs leading to withdrawal from study
- AEs related to investigational product
- AEs leading to death

Subjects will be counted only once at the system organ class level and once for each applicable preferred term; regardless of how many of those events they have had. Data will be sorted by descending frequency of system organ class, then descending frequency of preferred term within each system organ class for the GBR 830 group.

The count and percentage of AEs by severity will also be summarized. If severity is missing, AEs will be considered to be severe. If there are multiple severities for the same preferred term, the most severe will be used.

All AEs will be displayed in a two-part subject listing sorted by treatment group and including the following information:

- Part 1:
  - AE onset date/time and relative study day
  - AE end date/ time and relative study day
  - Duration of AE (days) [derived as: AE end date – AE start date +1 day]
  - Treatment emergent flag
  - SAE (Yes; No)
  - MedDRA body system
  - MedDRA preferred term
  - Investigator included term (verbatim)
  - Subject's age at baseline and sex
  - Time on treatment at the onset of the event [derived as: treatment start date – AE start date +1 day]

- Part 2:
  - Event severity: Mild; Moderate; Severe
  - Relationship to study treatment: Related; Not related
  - Action taken with study treatment: None; Permanently withdrawn, Temporary interrupted; Dose increased; Dose reduced
  - Other action taken: None; Concomitant Medication given; Withdrawn; Other
  - Outcome: Completely resolved; Resolved with sequelae; Improved; Ongoing; Worsened; Death; Unknown

9.1.2. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

All SAEs will be listed as above by treatment group (refer to Section 9.1.1).

The following criteria for the SAE will be included in this listing. The criteria are as follows:

- Fatal
- Life threatening
- Required inpatient hospitalization
- Hospitalization prolonged
- Persistent or significant disability or incapacity

- Congenital anomaly/birth defect
- Other medically significant event

9.2. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

On Visit 2 and Visit 7, the count and percentage of subjects who received any infusion of study treatment will be summarized by treatment group and overall. Descriptive statistics for the percentage compliance will be summarized at each visit and overall by treatment group and overall.

The daily percentage compliance for each subject will be derived as:

(actual volume administered / planned volume to be administered) x 100.

The total percentage compliance for each subject will also be calculated as:

(Visit 2 actual volume administered + Visit 7 actual volume administered) / (Visit 2 planned volume to be administered + Visit 7 planned volume to be administered) x 100.

For total percentage compliance, if a subject discontinues the study before their Visit 7, the actual and planned volume for Visit 7 will be both zero.

A subject listing will also be provided containing IV infusion data and compliance calculations.

9.3. Concomitant Medications and Non-Drug Treatments

Concomitant medications that subjects took after the baseline visit will be summarized by treatment group and overall. Concomitant medications will be coded using WHO DDE (September 2015).

A supportive subject listing will be provided including trade and generic drug names, start and stop dates, days relative to the start of treatment [derived as: Concomitant start date – treatment start date + 1 day], dose, frequency, route, and indication(s).

Concomitant non-drug treatment will also be summarized by treatment group and overall in a separate table and listing.

Rescue medications and treatments will be summarized in a separate table and listing to concomitant medications and concomitant non-drug treatment (see Section 9.8 for further details).

9.4. Routine Laboratory Data

Summary tables will be presented for each parameter [for a full list of laboratory parameters see below] by treatment group of the following of laboratory categories: Haematology, Serum

Biochemistry, Liver function tests, Renal function tests, Lipid Profile, Urinalysis, Serology, Other. Descriptive statistics will be used to summarize the data:

- Quantitative laboratory test result will include count, mean, s.d., median, minimum and maximum.
- Qualitative tests (e.g. some urinalysis assessments) will be categorized accordingly.

Analyses of the laboratory data will focus on the changes from baseline to each planned visit. For each laboratory test, there will be three sets of descriptive statistics that summarize the results at baseline, result at each visit, and the change from baseline to each visit. The final assessment available will also be summarized.

Shift tables will be included that summarize the count and percentage by laboratory parameter of the following categories:

- Abnormal, low
- Normal
- Abnormal, high
- Missing

Changes from baseline to the worst post-baseline values for each subject will be displayed. Unscheduled visits will be considered for the worst post baseline result. The following categories will also be presented if there is both an abnormal, low and abnormal, high shift post baseline.

- Abnormal, (low and high)

The supportive listings for hematology, serum chemistry, and urinalysis will include the sample collection date, time of collection, and relative day; type of visit; subject age at baseline and sex; and laboratory test, lab test units, and lab test result; and the lower and upper limits of normal.

9.4.1. Laboratory tests

The following laboratory tests will be summarized:

Haematology

- Haemoglobin (g/L)
- Hematocrit (V/V)
- White blood cell count (x10E9/L)
- Differential white cell count (%)
- Red blood cell count with mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration (x10E12/L)

- Platelets (x10E9/L)

Serum Biochemistry

- Electrolytes (TBC)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mmol/L)
- Chloride (mmol/L)
- Bicarbonate (mmol/L)

Liver function tests

- Total and direct bilirubin (umol/L)
- Total protein (g/L)
- Globulin (g/L)
- Albumin (g/L)
- AST (U/L)
- ALT (U/L)
- GGT (U/L)
- ALP (Alkaline phosphatase) (IU/L)
- Lactate dehydrogenase (U/L)

Renal function tests

- Creatinine (umol/L)
- Blood urea nitrogen (BUN) (mmol/L)

Other

- Fasting blood sugar (TBC)
- Serum FSH (female, only at screening) (IU/L)
- Serum and urine Beta-HCG (for females only) (N/A)
- Serum Immunoglobulins (TBC)

Lipid Profile

- Total cholesterol (mmol/L)
- Triglycerides (mmol/L)
- HDL (mmol/L)
- LDL (mmol/L)
- VLDL (mmol/L)

Urinalysis

- pH (N/A)
- Specific gravity (N/A)

Other

- QuantiFERON Gold Blood TB Test (N/A)
- Total IgE (kU/L)
- Circulating eosinophils count (TBC)

9.5. Vital Signs

Descriptive statistics will be used to summarize post baseline vital sign results and also changes from baseline by treatment group at each planned visit. Vital signs will be summarized at each visit and at 30 minute time points during infusion visits.

Descriptive statistics will be provided for the following vital sign parameters:

- Systolic blood pressure (mmHg)*
- Diastolic blood pressure (mmHg)*
- Body temperature (°C)
- Pulse rate (beats per minute [bpm])*
- Weight (kg)
- BMI (kg/m^2)

*Blood pressure and pulse rate is to be tested in supine or semi-supine position.

At each planned visit, blood pressure, body temperature and pulse rate will be categorized as normal; abnormal, not clinically significant; abnormal, clinically significant.

Shift tables will present changes from baseline to the worse post-baseline values for the following categories:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant
- Missing

Unscheduled visits will be considered for the worst post baseline result.

All vital signs data will be displayed in a subject listing and clinically significant findings will be flagged.

9.6. Physical Examination

The results of the brief physical examination will be summarized by treatment group. Summaries will be presented at baseline and for the worst post-baseline result only. The following body systems will be summarized:

- Thorax/Lungs
- Cardiovascular system
- Neurological examination
- Other

Each body system will be categorized into one of the following: normal; abnormal, not clinically significant; abnormal, clinically significant. The count and percentage of subjects in each category will be summarized by treatment group and overall. The count and percentage of subjects whose brief physical examination is not performed will also be summarized.

The body system data at each visit will be listed and clinically significant values will be flagged.

9.7. ECG

Subjects undergo a 12-lead ECG assessment either singularly or in triplicate at each planned visit. Triplicate ECGs are performed only if clinically significant abnormalities are detected in the subject's single ECG..

The change from baseline will be summarized at each planned visit by treatment group for single ECG. If there are multiple single, then the last available information for that parameter at that

visit will be used for the summary. The following measures will be reported using descriptive statistics:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTcF interval (ms)

For the overall interpretation of the ECGs at each visit, the count and percentage of subjects for each of the following categories will be reported by treatment group and overall:

- Normal
- Abnormal, non clinically significant
- Abnormal, clinically significant
- Missing

The QTc prolongations below will also be summarized by treatment group and overall:

- QTc interval at any visit > 500ms
- QTc interval increases from baseline > 60ms

For the analysis of the triplicate, the categorization will be derived using worst-case scenario rules such that the following order of precedence will be used: Abnormal, clinically significant; abnormal, non clinically significant; normal.

The ECG will also be listed and clinically significant values will be flagged.

9.8. Rescue Medication

Concomitant rescue medications/treatments will be summarized using counts and percentages by treatment group and overall.

Rescue medications/treatments will be coded by WHO DDE (September 2015) and the count and percentage of each preferred term (generic medication) will be summarized by treatment group and overall.

The data for each subject who received rescue medications will also be listed including the preferred term, dose/unit, route and frequency, start study day of rescue medication/treatment, duration of treatment and whether the treatment is ongoing.

9.9. Study Termination Status

The end of study status by treatment group is described as part of subject disposition (Section 7.1).

10. CLINICAL PHARMACOLOGY DATA ANALYSES

The Pharmacokinetic (PK) of GBR 830 in adult subjects with moderate to severe AD in terms of C_{max}, $AUC_{0\text{-}tau}$, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{½}$, volume of distribution and clearance will be assessed as relevant after the first and last doses.

All PK analysis will be performed on the Pharmacokinetic Analysis Set.

10.1. Pharmacokinetic/ Pharmacodynamic Analyses

PK parameters will be calculated from the GBR 830 concentration-time data using SAS v9.4. PK parameters will be estimated from the pre dose time point of each infusion, infusions will take place on Day 1 and 29. Measures will be taken within 15 minutes of administration of each dose (pre dose), immediately at the end of each infusion; then at, 1.5, 2, 4, 72, 168, 336, 504 hours after the start of each infusion; and on Day 57 (1344 hours from the first infusion), 71 (1680 hours), and 85 (2016 hours).

Partial or missing time point information will not be considered in the analysis.

Non-compartmental methods will be used to analyze the PK data. Actual sampling time points will be used for the calculation of PK parameters.

10.1.1. Dosing intervals

The dosing interval for the first IV infusion will consist of the following time points: pre dose, end of infusion; then at 1.5, 2, 4, 72, 168, 336, 504 hours from the start time of the first infusion, as well as pre dose for the second infusion.

The dosing interval for the second IV infusion will consist of the following time points: pre dose, end of the infusion; then at 1.5, 2, 4, 72, 168, 336, 504 hours from the start time of the second infusion, as well as Day 57. This time duration will be used for the calculation of $AUC_{0\text{-}tau}$.

In addition, PK samples are collected at day 71 and day 85. These data will be included in calculation of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$.

10.1.2. Analysis of Parameters

The parameters will be estimated for each dosing intervals as follows:

Table 2: PK Parameters

Parameter name	Description
C_{max}	Maximum observed Concentration after each dosing interval. This will be provided after each dosing event.

Parameter name	Description
T_{max}	Time at which C_{max} was observed. This will be provided after each dosing event.
$AUC_{0\text{-}tau}$	Trapezoid calculation of area under the serum drug concentration-time curve from time zero (pre dose time point of the infusion) to the end of the dosing interval. This will be provided after each dosing event.
$AUC_{0\text{-}t}$	Calculation of area under the serum drug concentration-time curve from time zero (pre dose time point of the infusion) to the last time point where quantifiable concentration is observed. This will be provided after each dosing event.
$AUC_{0\text{-}\infty}$	Total AUC computed by combining $AUC_{0\text{-}t}$ with extrapolated AUC. This will be provided after the second dosing event only.
%AUC extrapolated	Percentage extrapolated AUC; This will be provided after the second dosing event only. Only presented if %AUC extrapolated is less than $\leq$ 20%
λ_z	Terminal elimination rate constant. This will be provided after the second dosing event only. Linear regression of at least three points and an r^2 greater than 0.80 are required to retain λz and associated parameters $t_{1/2}$, V_d, $AUC_{0\text{-}\infty}$.
$t_{½}$	Half life This will be provided after the second dosing event only.
V_d	Observed apparent volume of distribution. This will be provided after the second dosing event only.
CL	Observed Clearance. This will be provided after the second dosing event only.
C_{trough}	Trough concentration. Concentration at 672 hours after each infusion (day 29 and day 57)

Elimination Rate

Initially to estimate the elimination rate coefficient a linear regression model will be fitted to the individual $\log_{10}$ elimination phase concentration values. The elimination phase is defined between maximum observed concentration and last observed value above the LLOQ. The elimination rate constant is defined as

$$\lambda_z = -2.303 \times \text{slope}$$

Half life (calculated only after second dose)

$$t_{½} = \frac{0.693}{\lambda_z}$$

Area under the curve to the last measurable concentration (after each dosing interval)

$$AUC_{0-t} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i + C_{i+1})$$

Where n is the number of data points.

The area under the concentration curve from time '0' to up to the last time point where quantifiable serum concentrations were observed will be calculated separately for both the dosing occasions. The start time of infusion, for each dosing occasion, would be considered as time '0' for the calculation of $AUC_{0\text{-}t}$. The pre dose serum concentration (concentration in the sample collected closest to the start of infusion) would be considered as the concentration at time '0'. The last data point considered for the calculation of $AUC_{0\text{-}t}$ after the 1st dosing event would be the pre dose serum concentrations on day 29 and after 2nd dosing event would be the serum concentration on day 85, respectively. If the data point is not available on either of these occasions, the closest time point where the serum concentrations are available would be used for the calculation of $AUC_{0\text{-}t}$.

Area under the curve over the dosing interval (after each dosing event)

$$AUC_{0-tau} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i + C_{i+1})$$

Where n is the number of data points in each interval.

The area under the concentration curve for each dosing interval would be calculated separately after each dosing occasion. The start time of infusion, for each dosing occasion, would be considered as time '0' for the calculation of $AUC_{0\text{-}tau}$. The pre-dose serum concentration (concentration in the sample collected closest to the start of infusion) would be considered as the concentration at time '0'. The last data point considered for calculation of $AUC_{0\text{-}tau}$ after the 1st dosing event would be the pre dose serum concentrations on day 29 and after 2nd dosing event would be the serum concentration on day 57, respectively. If the data point is not available on either of these occasions, the closest time point where the serum concentrations are available would be used for the calculation of $AUC_{0\text{-}tau}$.

Area under the curve extrapolated to infinity (calculated only after second dose)

$$AUC_{\infty} = AUC_{0-t} + \frac{C_n}{\lambda_z}$$

Observed Volume of Distribution at steady state (calculated only after second dose)

$$V_d = \frac{\mathrm{D}}{AUC_{0-tau\times}\lambda_z}$$

(Where D is actual dose received)

Observed Clearance (calculated only after second dose)

$$CL = \frac{D}{AUC_{0-tau}}$$

(Where D is actual dose received)

10.1.3. Handling of values below the limit of quantification

When the value that is recorded as below the limit of quantification (BLQ), this will be treated as either zero or missing dependant upon when the BLQ value was observed relative to other non BLQ values. Details are below.

- The BLQ value before the beginning of the infusion (Pre dose) will be set to zero.
- All BLQ values observed between the start of infusion and the first observed concentration will be treated as zero
- If a single BLQ value is observed at a time between two non-zero observations it will be treated as missing.
- When two or more BLQ consecutive values are observed these will be treated as zero until the next observed non-zero value.
- All BLQ values after the last measurable observation (C_n) after each dosing will be treated as zero.

These rules will be applied to the estimation of individual PK parameters detailed above and in the calculation of summary statistics for serum concentration levels and the plot of mean concentration curves. For semi-log plots all BLQ values will be set to missing.

10.1.1. Treatment of outliers

Individual concentration time points or entire individual treatment profiles, if considered anomalous, may be excluded from the analysis at the discretion the pharmacokineticist following a review of the available documentation. Any such exclusion will be clearly outlined in the CSR.

11. CHANGES FROM THE PLANNED PROTOCOL ANALYSIS

11.1. Shift Tables

All shift tables will now be presented as baseline to worst post baseline visit, rather than on a by visit basis.

11.2. Exploratory Cytokines Analysis

Cytokines will now be analyzed post data base lock.

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[4]	x													
Demographics (incl. height, weight and BMI)[5]	x	x					x							x
Physical examination[6]	x	x			x		x			x				x
TB testing[7]	x													
Vital signs[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG[9]	x	x	x	x			x	x	x			x	x	x
Clinical laboratory[10]	x	x	x	x			x	x	x			x	x	x
Drug and alcohol screen[11]	x	x					x							
HBsAg, Anti-HBc Ag, HCV and HIV tests	x													
Serum pregnancy (females only)[12]	x	x												x
Urine pregnancy (females only)[13]		x					x							
EASI, SCORAD, IGA, BSA[14,15]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole body photography[16]		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[11]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Phone call[11]		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 subjects 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 subjects 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: Subjects 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 women will be done during screening, Day 1 and at the end of study.

11. Urine pregnancy test for 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 subject 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 subject 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. Subject must enter data into the diary every day from start of screening period to end of study visit. Subject will be trained on the use of diary. Subject 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 subjects by telephone approximately 24 hours after each infusion of IP.

17. Serum samples for GBR-830 PK analysis will be obtained 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 subject 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. TABLE OF CONTENTS FOR DATA DISPLAY SPECIFICATIONS

Title		Analysis set	Comments (*subject to request)	New table number*
Study Population Section				
Table 14.1.1	Subject Disposition	Screened Subjects	Unique	Table 14.1.1
Table 14.1.2	Analysis Sets	Randomized Subjects	Unique	Table 14.1.2
Table 14.1.3	Study Participation	Full Analysis Set	Unique	Table 14.1.3
Table 14.2.1.1	Demographic Characteristics	Full Analysis Set	Unique	Table 14.1.4.1.1
Table 14.2.1.2	Demographic Characteristics	Biological Activity Set	Repeat	Table 14.1.4.1.2
Table 14.2.1.3	Demographic Characteristics	Pharmacokinetic Analysis Set	Repeat	Table 14.1.4.1.3
Table 14.2.2	Atopic Dermatitis (AD) History	Full Analysis Set	Unique	Table 14.1.4.2
Table 14.2.3	Medical/Surgical History	Full Analysis Set	Unique	Table 14.1.4.3
Table 14.2.4	Smoking, Alcohol and Drug Abuse History	Full Analysis Set	Unique	Table 14.1.4.4
Table 14.2.5.1	Atopic Dermatitis and Related Conditions Baseline Prior Medications	Full Analysis Set	Unique	Table 14.1.5.1
Table 14.2.5.2	Other Baseline Prior Medications	Full Analysis Set	Repeat	Table 14.1.5.2
Table 14.2.10	Baseline Clinical Scores	Full Analysis Set	Unique	Table 14.1.6
Table 14.2.11.1	Baseline Active AD mRNA Expression Signatures Obtained from Skin Biopsies (Non Lesion Samples)	Biological Activity Set	Repeat	Table 14.1.7.1
Table 14.2.11.2	Baseline Pathologic Epidermal Phenotype Measures Obtained from Skin Biopsies (Non Lesion Samples)	Biological Activity Set	Repeat	Table 14.1.7.2
Efficacy Section				
Tables				

Title		Analysis set	Comments (*subject to request)	New table number*
14.3.1.1a	MMRM Analysis Selected Active AD mRNA Expressions (Normalized to hARP) Obtained from Skin Biopsies (Lesion Samples)- Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.1a
Table 14.3.1.1b	Change from Baseline in the Selected Active AD mRNA Expression Signatures (Normalized to hARP) Obtained from Skin Biopsies by Lesion Location –Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.1b
Table 14.3.1.2	Change from Baseline in H&E Thickness Obtained from Skin Biopsies by Lesion Location – Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.2
Table 14.3.1.3	Summary of K16 Obtained from Skin Biopsies by Lesion Location and Visit – Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.3
Table 14.3.1.4	Summary of Histological Response Obtained from Skin Biopsies by Lesion Location and Visit – Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.4
Table 14.3.1.5	Summary of IHC Panel from Skin Biopsies by Visit – Primary Analysis	Biological Activity Set	Unique	Table 14.2.1.4
Table 14.2.2	Proportion of Subjects who Achieved an IGA Score of 0 or 1 by Visit	Biological Activity Set	Unique	Table 14.2.2
Table 14.3.3.1	Proportion of Subjects who Achieved an EASI 50 Response by Visit	Full Analysis Set	Unique	Table 14.2.3.1
Table 14.3.3.2	Proportion of Subjects who Achieved an EASI 75 Response by Visit	Full Analysis Set	Repeat	Table 14.2.3.2
Table 14.3.3.3	Analysis of Covariance (ANCOVA) of change from baseline in EASI Score to Visit 12 LOCF	Full Analysis Set	Unique	Table 14.2.3.3
Table 14.3.4.1	Percent Change from Baseline in EASI Clinical Score at Each Visit	Full Analysis Set	Unique	Table 14.2.4.1
Table 14.3.4.2	Percent change from Baseline in SCORAD Clinical Score at Each Visit	Full Analysis Set	Repeat	Table 14.2.4.2
Table 14.3.4.3	Percent Change from Baseline in IGA Clinical Score at Each Visit	Full Analysis Set	Repeat	Table 14.2.4.3
Table 14.3.4.4	Percent change from Baseline in Pruritus NRS Clinical Score at Each Visit	Full Analysis Set	Repeat	Table 14.2.4.4
Table 14.3.4.5	Percent change from Baseline in DLQI Clinical Score at Each Visit	Full Analysis Set	Repeat	Table 14.2.4.5
Table 14.3.5	Changes from Baseline in Transepidermal Water Loss (g/m2/h) by Lesion/Non-Lesion Area	Full Analysis Set	Unique	Table 14.2.5
Table 14.3.6	Anti-Drug Antibodies to GBR 830 by Visit	Full Analysis Set	Unique	Table 14.2.6

Title		Analysis set	Comments (*subject to request)	New table number*
Table 14.3.8	Changes from Baseline in Leukocytes Sub-Population Cell Counts	Full Analysis Set	Unique*	Table 14.2.7
Table 14.3.9	Changes from Baseline in Cellular Infiltrates	Full Analysis Set	Repeat*	Table 14.2.8
Table 14.3.10	Changes from Baseline in Serum Total Immunoglobulin E, Serum Soluble OX40, Serum Soluble OX40 and Circulating Eosinophil Counts	Full Analysis Set	Repeat*	Table 14.2.9
Table 14.3.12	Prohibited Medications	Full Analysis Set	Unique	Table 14.2.10
Safety Section				
Tables				
Table 14.4.1	Overall Treatment Emergent Adverse Events	Safety Analysis Set	Unique	Table 14.3.1.1.1
Table 14.4.2.1	Treatment Emergent Adverse Events	Safety Analysis Set	Unique	Table 14.3.1.1.2
Table 14.4.2.2	Serious Treatment Emergent Adverse Events	Safety Analysis Set	Repeat	Table 14.3.1.2
Table 14.4.2.5	Treatment Emergent Adverse Events Leading to Discontinuation of Study	Safety Analysis Set	Repeat	Table 14.3.1.3
Table 14.4.2.6	Treatment Emergent Adverse Events Related to the Investigational Product	Safety Analysis Set	Repeat	Table 14.3.1.4
Table 14.4.2.7	Treatment Emergent Adverse Events Leading to Death	Safety Analysis Set	Repeat	Table 14.3.1.5
Table 14.4.2.8	Treatment Emergent Adverse Events by Severity	Safety Analysis Set	Unique	Table 14.3.1.6
Table 14.4.3	Study Drug Treatment Compliance	Safety Analysis Set	Unique	Table 14.3.6.1.1
Table 14.4.4.1	Concomitant Medications for Atopic Dermatitis and Related Conditions	Safety Analysis Set	Unique	Table 14.3.6.2.1
Table 14.4.4.2	Concomitant Non-Drug Treatments	Safety Analysis Set	Repeat	Table 14.3.6.2.2
Table 14.4.4.3	Rescue Medications	Safety Analysis Set	Repeat	Table 14.3.6.2.3
Table 14.4.5.1	Change from Baseline in Laboratory Results by Category	Safety Analysis Set	Unique	Table 14.3.5.1
Table 14.4.5.2	Shift Table of Laboratory Results from Baseline to Worst Post Baseline Result by Category and Treatment Group	Safety Analysis Set	Unique	Table 14.3.5.2
Table 14.4.6.1	Change from Baseline in Vital Signs Results	Safety Analysis Set	Unique	Table 14.3.6.3.1

Title		Analysis set	Comments (*subject to request)	New table number*
Table 14.4.6.2	Shift Table of Vital Signs from Baseline to Worst Post Baseline Result by Treatment Group	Safety Analysis Set	Unique	Table 14.3.6.3.2
Table 14.4.7	Physical Examination Results	Safety Analysis Set	Unique	Table 14.3.6.4
Table 14.4.8.1	Change from Baseline in Electrocardiogram Results	Safety Analysis Set	Unique	Table 14.3.6.5.1
Table 14.4.8.2	Overall Interpretations of Electrocardiogram	Safety Analysis Set	Unique	Table 14.3.6.5.2
Table 14.4.9	GBR830 Serum Concentration (ng/mL) Data	Pharmacokinetic Analysis Set	Unique	Table 14.3.6.7
Table 14.4.10	Pharmacokinetic Parameters of GBR830	Pharmacokinetic Analysis Set	Unique	Table 14.2.10.1
Figures				
Figure 14.3.1.1	Box plot of biomarker CCL11/hARPby Planned Treatment Group	Biological Activity Set	Unique	Figure 14.2.1
Figure 14.3.3.1	Line Plot of EASI 50 Responders over Time (days) by Planned Treatment Group	Full Analysis Set	Unique	Figure 14.2.2
Figure 14.3.4.1	Line Plot of Mean ± SE Percentage Change in EASI Score over Time (days) by Planned Treatment Group	Full Analysis Set	Repeat	Figure 14.2.3
Figure 14.3.4.4	Line Plot of Mean ± SE Percentage Change in Pruritus NRS over Time (days) by Planned Treatment Group	Full Analysis Set	Repeat	Figure 14.2.4
Figure 14.3.6.1	Scatter Plot of Serum Concentration (µg/mL) over Anti Drug Antibody Status by Planned Treatment Group	Pharmacokinetic Analysis Set	Unique	Figure 14.2.5
Figure 14.4.11.1	Mean Serum GBR830 Concentration Data (0 to 2016 hours) Overall	Pharmacokinetic Analysis Set	Unique	Figure 14.2.6.1
Figure 14.4.11.2	Individual Subject Profiles of Serum GBR830 Concentration Data (0 to 2016 hours)	Pharmacokinetic Analysis Set	Unique	Figure 14.2.6.2

*New number will be used in final displays

Listings

Title		Population	Comment	New Number*
Listing 16.1.1	Subject Disposition	Randomized Subjects	Unique	Listing 16.2.1.1
Listing 16.1.2	Analysis Populations	Screened Subjects	Unique	Listing 16.2.3.1
Listing 16.1.3	Subject Inclusion/Exclusion Criteria	Screened Subjects	Unique	Listing 16.2.1.2
Listing 16.1.4	Screen Failure Subjects	Screened Subjects	Unique	Listing 16.2.1.3
Listing 16.1.5	Subject Randomization Information	Randomized Subjects	Unique	Listing 16.1.7
Listing 16.2.1.1.1	Subject Demographic and Baseline Characteristics – Part 1	Randomized Subjects	Unique	Listing 16.2.4.1
Listing 16.2.1.1.2	Subject Demographic and Baseline Characteristics – Part 1	Screen Failure Subjects	Repeat	Listing 16.2.4.2
Listing 16.2.1.2.1	Subject Demographic and Baseline Characteristics – Part 2	Randomized Subjects	Unique	Listing 16.2.4.3
Listing 16.2.1.2.2	Subject Demographic and Baseline Characteristics – Part 2	Screen Failure Subjects	Repeat	Listing 16.2.4.4
Listing 16.2.2	Atopic Dermatitis History	Randomized Subjects	Unique	Listing 16.2.4.5
Listing 16.2.3	Medical/Surgical History	Randomized Subjects	Unique	Listing 16.2.4.6
Listing 16.2.4.1	Smoking, Alcohol and Drug Abuse History – Part 1	Randomized Subjects	Unique	Listing 16.2.4.7
Listing 16.2.4.2	Smoking, Alcohol and Drug Abuse History – Part 2	Randomized Subjects	Unique	Listing 16.2.4.8
Listing 16.2.5.1	Atopic Dermatitis and Related Conditions Baseline Prior Medications	Randomized Subjects	Unique	Listing 16.2.4.9.1
Listing 16.2.5.2	Other Baseline Prior Medications	Randomized Subjects	Repeat	Listing 16.2.9.4
Listing 16.2.6	Baseline Physical Examination	Randomized Subjects	Unique	Listing 16.2.9.5

Title		Population	Comment	New Number*
Listing 16.3.1	Active AD mRNA Expression Signature and Pathologic Epidermal Phenotype Measures	Full Analysis Set	Unique	Listing 16.2.6.1
Listing 16.3.2	IGA Scores	Full Analysis Set	Unique	Listing 16.2.6.2
Listing 16.3.3	EASI Scores	Randomized Subjects	Unique	Listing 16.2.6.3
Listing 16.3.4.1	SCORAD Clinical Scores	Full Analysis Set	Unique	Listing 16.2.6.4
Listing 16.3.4.4	Pruritus NRS Clinical Scores	Full Analysis Set	Repeat	Listing 16.2.6.5
Listing 16.3.4.5	DLQI Clinical Scores	Full Analysis Set	Repeat	Listing 16.2.6.6
Listing 16.3.5	Transepidermal Water Loss Readings	Full Analysis Set	Unique	Listing 16.2.6.7
Listing 16.3.6	Anti-Drug Antibodies (ADA)	Safety Analysis Set	Unique	Listing 16.2.6.8
Listing 16.3.8	Leukocytes Sub-Population Cell Counts	Full Analysis Set	Unique*	Listing 16.2.6.9
Listing 16.3.9	Cellular Infiltrates	Full Analysis Set	Repeat*	Listing 16.2.6.10
Listing 16.3.10	Serum Total Immunoglobulin E, Serum Soluble OX40, Serum Soluble OX40 and Circulating Eosinophil Counts	Full Analysis Set	Repeat*	Listing 16.2.6.11
Listing 16.3.12	Prohibited Medications	Full Analysis Set	Unique	Listing 16.2.2.2
Listing 16.4.1.1.1	Adverse Events – Part 1	Safety Analysis Set	Unique	Listing 16.2.7.1
Listing 16.4.1.2.1	Serious Adverse Events – Part 1	Safety Analysis Set	Repeat	Listing 16.2.7.3
Listing 16.4.1.5.1	Adverse Events Leading to Discontinuation of Study – Part 1	Safety Analysis Set	Repeat	Listing 16.2.7.5
Listing 16.4.1.7.1	Adverse Events Leading to Death – Part 1	Safety Analysis Set	Repeat	Listing 16.2.7.7
Listing 16.4.1.1.2	Adverse Events – Part 2	Safety Analysis Set	Unique	Listing 16.2.7.2
Listing	Serious Adverse Events – Part 2	Safety Analysis Set	Repeat	Listing

Title		Population	Comment	New Number*
16.4.1.2.2				16.2.7.4
Listing 16.4.1.5.2	Adverse Events Leading to Discontinuation of Study – Part 2	Safety Analysis Set	Repeat	Listing 16.2.76
Listing 16.4.1.7.2	Adverse Events Leading to Death – Part 2	Safety Analysis Set	Repeat	Listing 16.2.7.8
Listing 16.4.2	Study Drug Administration	Safety Analysis Set	Unique	Listing 16.2.5.1
Listing 16.4.3.1	Concomitant Medications	Safety Analysis Set	Unique	Listing 16.2.5.2
Listing 16.4.3.2	Concomitant Non-Drug Therapies	Safety Analysis Set	Unique	Listing 16.2.5.3
Listing 16.4.3.3	Rescue Medications	Safety Analysis Set	Repeat	Listing 16.2.5.4
Listing 16.4.4.1.1	Heamatology Results	Safety Analysis Set	Unique	Listing 16.2.8.1
Listing 16.4.4.1.2	Subjects with Abnormal Hematology Results	Safety Analysis Set	Repeat	Listing 16.2.8.2
Listing 16.4.4.2.1	Serum Biochemistry Results	Safety Analysis Set	Repeat	Listing 16.2.8.3
Listing 16.4.4.2.2	Subjects with Abnormal Serum Biochemistry Results	Safety Analysis Set	Repeat	Listing 16.2.8.4
Listing 16.4.4.3	Urinalysis Results	Safety Analysis Set	Repeat	Listing 16.2.8.5
Listing 16.4.4.4	Serology Results	Safety Analysis Set	Repeat	Listing 16.2.8.6
Listing 16.4.4.5	Other Laboratory Test Results	Safety Analysis Set	Repeat	Listing 16.2.8.7
Listing 16.4.5	Vital Signs Results	Safety Analysis Set	Unique	Listing 16.2.9.1
Listing 16.4.6	Brief Physical Examination	Safety Analysis Set	Unique	Listing 16.2.9.2
Listing 16.4.7	Electrocardiogram (ECG) Results	Safety Analysis Set	Unique	Listing 16.2.9.3
Listing 16.4.8	Individual GBR830 Serum Concentration (ng/mL) Data	Pharmacokinetic Analysis Set	Unique	Listing 16.2.6.12
Listing 14.4.9	Individual Pharmacokinetic Parameters of GBR830	Pharmacokinetic Analysis Set	Unique	Listing 16.2.6.13
Listing 16.4.10	Time Points used to Calculate the GBR830 Elimination Rate Constant (λz)	Pharmacokinetic Analysis Set	Unique	Listing 16.2.6.14

Title		Population	Comment	New Number*
Listing 16.4.11	Reasons Pharmacokinetic Parameters Could Not be Determined	Pharmacokinetic Analysis Set	Unique	Listing 16.2.6.15
Listing 16.5.2	Protocol Deviations	Randomized Subjects	Unique	Listing 16.2.2.1

*New number is used in final displays

APPENDIX 3. DATA DISPLAY SPECIFICATIONS

Table 14.1.1
Subject Disposition
Screened Subjects

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Subjects screened	n			x
Screen failures	n			x
Re-screened	n			x
Subjects randomized	n (%)	x (100)	x (100)	x (100)
Subjects replaced	n (%)	x (xxx)	x (xxx)	x (xxx)
End of study status				
Subject completed study	n (%)	x (xxx)	x (xxx)	x (xxx)
Subject withdrawn	n (%)	x (xxx)	x (xxx)	x (xxx)
Reason for early termination/withdrawal				
Withdrawal of consent	n (%)	x (xxx)	x (xxx)	x (xxx)
Adverse event	n (%)	x (xxx)	x (xxx)	x (xxx)
Investigator's discretion	n (%)	x (xxx)	x (xxx)	x (xxx)
Non compliance with study procedures / protocol deviation	n (%)	x (xxx)	x (xxx)	x (xxx)
Pregnancy	n (%)	x (xxx)	x (xxx)	x (xxx)
Subjects requiring rescue medications or interventions/treatment with another therapeutic agent	n (%)	x (xxx)	x (xxx)	x (xxx)
Disease progression/exacerbation	n (%)	x (xxx)	x (xxx)	x (xxx)
Subjects randomized in the study who withdraw their consent for the first post-baseline skin biopsies	n (%)	x (xxx)	x (xxx)	x (xxx)
Lost to follow up	n (%)	x (xxx)	x (xxx)	x (xxx)
Death	n (%)	x (xxx)	x (xxx)	x (xxx)
Other	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of randomized subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Table 14.1.2
Analysis Sets
Randomized Subjects

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Full Analysis Set (FAS)				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Biological Activity Set (BAS)				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Safety Analysis Set (SAF)				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Pharmacokinetic Analysis Set (PKAS)				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of randomized subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Table 14.1.3
Study Participation
Full Analysis Set

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Time on study (days)	N	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Number of subjects with any data at each visit				
Visit 2 (day 1)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 3 (day 4)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 4 (day 8)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 5 (day 15)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 6 (day 22)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 7 (day 29)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 8 (day 32)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 9 (day 36)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 10 (day 43)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 11 (day 50)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 12 (day 57)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 13 (day 71)	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 14/EOS (day 85/Early Termination)	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.1.1
Demographic Characteristics
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Age at study entry (years)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Age group at study entry				
<65 years	n (%)	x (xxx)	x (xxx)	x (xxx)
≥65 years	n (%)	x (xxx)	x (xxx)	x (xxx)
Sex				
Female	n (%)	x (xxx)	x (xxx)	x (xxx)
Male	n (%)	x (xxx)	x (xxx)	x (xxx)
Race				
Asian	n (%)	x (xxx)	x (xxx)	x (xxx)
Black	n (%)	x (xxx)	x (xxx)	x (xxx)
White	n (%)	x (xxx)	x (xxx)	x (xxx)
American Indian or Alaska Native	n (%)	x (xxx)	x (xxx)	x (xxx)
Native Hawaiian or Other Pacific Islander	n (%)	x (xxx)	x (xxx)	x (xxx)
Other	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Table 14.2.1.1
Demographic Characteristics
Full Analysis Set

Cont.

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Ethnicity				
Hispanic or Latino	n (%)	x (xxx)	x (xxx)	x (xxx)
Not Hispanic or Latino	n (%)	x (xxx)	x (xxx)	x (xxx)
Weight (kg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Height (cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
BMI (kg/m^2)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Table 14.2.1.1
Demographic Characteristics
Full Analysis Set

Cont.

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Body surface area (m^2)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Country				
USA	n (%)	x (xxx)	x (xxx)	x (xxx)
Canada	n (%)	x (xxx)	x (xxx)	x (xxx)
Child bearing potential (female only)	N*	xxx	xxx	xxx
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Post menopausal	n (%)	x (xxx)	x (xxx)	x (xxx)
Duration of non child bearing potential ≤ 1 year	n (%)	x (xxx)	x (xxx)	x (xxx)
Duration of non child bearing potential > 1 year	n (%)	x (xxx)	x (xxx)	x (xxx)
Permanently sterilized	n (%)	x (xxx)	x (xxx)	x (xxx)
Duration of non child bearing potential ≤ 1 year	n (%)	x (xxx)	x (xxx)	x (xxx)
Duration of non child bearing potential > 1 year	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group. N* is the number of female subjects. Percentages of child bearing potential are based on N*.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Table 14.2.1.2
Demographic Characteristics
Biological Activity Set

Table 14.2.1.3
Demographic Characteristics
Pharmacokinetic Analysis Set

Table 14.2.2
Atopic Dermatitis (AD) History
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Years since AD diagnosis (years)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Years since AD diagnosis category				
<2 Years	n (%)	x (xxx)	x (xxx)	x (xxx)
2 – 5 Years	n (%)	x (xxx)	x (xxx)	x (xxx)
>5 Years	n (%)	x (xxx)	x (xxx)	x (xxx)
Age at AD diagnosis (years)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Type of AD				
Intrinsic	n (%)	x (xxx)	x (xxx)	x (xxx)
Extrinsic	n (%)	x (xxx)	x (xxx)	x (xxx)
Any history of allergy?				
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Was patch test performed?				
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
No	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.2
Atopic Dermatitis (AD) History
Full Analysis Set

Cont.

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Any other concomitant atopic illness?				
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Asthma	n (%)	x (xxx)	x (xxx)	x (xxx)
Allergic rhinitis	n (%)	x (xxx)	x (xxx)	x (xxx)
Skin conditions	n (%)	x (xxx)	x (xxx)	x (xxx)
Other	n (%)	x (xxx)	x (xxx)	x (xxx)
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Was skin biopsy performed in past?				
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Eosinophilic	n (%)	x (xxx)	x (xxx)	x (xxx)
Non-Eosinophilic	n (%)	x (xxx)	x (xxx)	x (xxx)
Other	n (%)	x (xxx)	x (xxx)	x (xxx)
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Any treatment administered for AD or associated condition?				
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
No	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.3
Medical/Surgical History
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
HEENT				
Preferred term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 2	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 3	n (%)	x (xxx)	x (xxx)	x (xxx)
Etc				

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group. Preferred terms are sorted in descending order by the overall column.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming notes: Also include the following body systems Cardiovascular System, Respiratory System, Musculoskeletal System, Dermatological System, Skin and its appendages, Lymphatic System, Gastrointestinal System, Genitourinary System, Nervous System, Endocrine System, Immunological System, Allergic Conditions, Other.

Table 14.2.4
Smoking, Alcohol and Drug Abuse History
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Former or current alcohol user				
N/A	n (%)	x (xxx)	x (xxx)	x (xxx)
Former	n (%)	x (xxx)	x (xxx)	x (xxx)
Current	n (%)	x (xxx)	x (xxx)	x (xxx)
Alcohol consumption (ml/week)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
History or alcohol abuse?				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Former or current drug user				
N/A	n (%)	x (xxx)	x (xxx)	x (xxx)
Former	n (%)	x (xxx)	x (xxx)	x (xxx)
Current	n (%)	x (xxx)	x (xxx)	x (xxx)
Is drug use clinically significant in the opinion of the Investigator or meets DSM-V criteria for addiction or abuse?				
No	n (%)	x (xxx)	x (xxx)	x (xxx)
Yes	n (%)	x (xxx)	x (xxx)	x (xxx)
Former or current smoker				
N/A	n (%)	x (xxx)	x (xxx)	x (xxx)
Former	n (%)	x (xxx)	x (xxx)	x (xxx)
Current	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.4
Smoking, Alcohol and Drug Abuse History
Full Analysis Set

Cont.

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Cigarettes per day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Former or current smokeless tobacco user				
N/A	n (%)	x (xxx)	x (xxx)	x (xxx)
Former	n (%)	x (xxx)	x (xxx)	x (xxx)
Current	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: 1.Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.5.1
Atopic Dermatitis and Related Conditions Baseline Prior Medications
Full Analysis Set

ATC Level 1 **ATC Level 2** **ATC Level 3** **ATC Level 4** **Preferred Term**	**Statistic**	**GBR 830 (N=xx)**	**Placebo (N=xx)**	**Overall (N=xx)**
ATC Level 1				
ATC Level 2				
ATC Level 3				
ATC Level 4				
Preferred term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 2	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 3	n (%)	x (xxx)	x (xxx)	x (xxx)
Etc				

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group. Preferred terms within the ATC Code are sorted in descending order by the overall column.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Repeat for:

Table 14.2.5.2
Other Baseline Prior Medications
Full Analysis Set

Table 14.2.10
Baseline Clinical Scores
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Eczema Area and Severity Index (EASI)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Investigator's Global Assessment (IGA)				
Severe	n (%)	x (xxx)	x (xxx)	x (xxx)
Moderate	n (%)	x (xxx)	x (xxx)	x (xxx)
Mild	n (%)	x (xxx)	x (xxx)	x (xxx)
Almost clear	n (%)	x (xxx)	x (xxx)	x (xxx)
Clear	n (%)	x (xxx)	x (xxx)	x (xxx)
Not done	n (%)	x (xxx)	x (xxx)	x (xxx)
Scoring of Atopic Dermatitis (SCORAD)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Dermatology Life Quality Index (DLQI)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.2.10
Baseline Clinical Scores
Full Analysis Set

cont.

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Pruritis Numerical Rating Scale (NRS)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

Footnote: Percentages are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Table 14.2.11.1
Baseline Active AD mRNA Expression Signatures Obtained from Skin Biopsies (Non Lesion Samples)
Biological Activity Set

Programming notes 1) Present baseline visit only, Repeat for all biomarkers

Table 14.2.11.2
Baseline Pathologic Epidermal Phenotype Measures Obtained from Skin Biopsies (Non Lesion Samples)
Biological Activity Set

Programming notes 1) Present baseline visit only, Repeat for all phenotypes

Table 14.3.1.1.a
MMRM Analysis Selected Active AD mRNA Expressions (Normalized to hARP) Obtained from Skin Biopsies (Lesion Samples)- Primary Analysis
Biological Activity Set

Biomarker: CCL18/hARP

Cont.

	GBR 830 (N=xx)	Placebo (N=xx)
Geometric LS mean of P/B ratio [2] (95% CI)	xx.x (xx.xx, xx.xx)	xx.x (xx.xx, xx.xx)
Ratio GBR830/placebo [3]:	xx.x (xx.xx, xx.xx)	
Adjusted LS mean treatment difference (95% CI)		
p-value	x.xxx	

Footnote:
[1] Geometric mean is exponentially back-transformed from the least squares (LS) mean based on a mixed model. It is presented on the original scale. The same transformation is applied in order to obtain the 95% CI.
[2] Mixed model with treatment group and planned visit as fixed effects, log transformed baseline value as covariate, and with treatment by visit interaction and unstructured covariance structure. Using log transformed mRNA values.
Ratio: P/B = Post-baseline / Baseline; CI = Confidence interval.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes: repeat table for all the log transformed biomarkersnormalized to hARP in the SAP text CCL11/hARP, CCL17/hARP, CCL18/hARP, CCL26/hARP, CXCL10/hARP, FOXP3/hARP, IFNg/hARP, IL23p40/hARP, IL5/hARP, IL13/hARP, IL17A/hARP, IL22/hARP, IL23p19/hARP, K16/hARP, MMP12/hARP, OX40L/hARP, S100A12/hARP, S100A9/hARP, TSLPR/hARP

Table 14.3.1.1.b
Change from Baseline in the Selected Active AD mRNA Expression Signatures (Normalized to hARP) Obtained from Skin Biopsies by Lesion Location –Primary Analysis
Biological Activity Set

Biomarker: CCL18/hARP

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	N	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)
Visit 7 (day 29)	N	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)
Change from Baseline to Visit 7 (day 29)	N	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
… (repeat for Visit 13 (day 71))	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)

[1] The geometric mean is presented on the original non transformed scale. All other statistics are presented on the log scale unless otherwise stated.
SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Programming notes: the summary (n, mean, SD, median, min, max) will be on the normalize gene without log transformation, repeat table for all mRNA normalized to hARP parameters in the SAP text and produce for lesion and non-lesion samples (if available)

Table 14.3.1.2
Change from Baseline in H&E Thickness Obtained from Skin Biopsies by Lesion Location – Primary Analysis
Biological Activity Set

Location: Lesion

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 7 (day 29)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 7 (day 29)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes 1) Repeat for appropriate non lesion.

Table 14.3.1.3
Summary of K16 Obtained from Skin Biopsies by Lesion Location and Visit – Primary Analysis
Biological Activity Set

Location: Lesion

		Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	Slight	n (%)	xx	xx
	Good	n (%)	xx	xx
	Excellent	n (%)	xx	xx
Visit 7 (day 29)	Worsening	n (%)	xx	xx
	No change	n (%)	xx	xx
Visit 13 (day 71)	Worsening	n (%)	xx	xx
	No change	n (%)	xx	xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes 1) Repeat for appropriate non lesion.

Table 14.3.1.4
Summary of Histological Response Obtained from Skin Biopsies by Lesion Location and Visit – Primary Analysis
Biological Activity Set

Location: Lesion

		Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	Responder	n (%)	xx	xx
	Non responder	n (%)	xx	xx
Visit 7 (day 29)	Responder	n (%)	xx	xx
	Non responder	n (%)	xx	xx
Visit 13 (day 71)	Responder	n (%)	xx	xx
	Non responder	n (%)	xx	xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes 1) Repeat for appropriate non lesion.

Table 14.2.1.5
Summary of IHC Panel from Skin Biopsies by Visit – Primary Analysis
Biological Activity Set

Parameter: CD3 Epidermis # of Cells per 1.2m

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)
Visit 7 (day 29)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)
Change from Baseline to Visit 7 (day 29)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	Xx
	Max.	xx	xx
	Geometric mean (%CV) [1]	xx.x (xx.xx)	xx.x (xx.xx)

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Programming notes 1) Repeat for appropriate non lesion.Parameters summarized will include: CD3.EPIDERMIS # of Cells per 1.2mm2 , CD3.DERMIS # of Cells per 1.2mm2, Ki67.EPIDERMIS # of Cells per 1.2mm2 , Ki67.DERMIS # of Cells per 1.2mm2 , FcEpsilonRI.DERMIS # of Cells per 1.2mm2 , FcEpsilonRI.EPIDERMIS # of Cells per 1.2mm2 , OX40.EPIDERMIS # of Cells per 1.2mm2, OX40.DERMIS # of Cells per 1.2mm2 , OX40L.EPIDERMIS # of Cells per 1.2mm2 , OX40L.DERMIS # of Cells per 1.2mm2, MBP.EPIDERMIS # of Cells per 1.2mm2 , MBP.DERMIS # of Cells per 1.2mm2

Table 14.3.2
Proportion of Subjects who Achieved an IGA Score of 0 or 1 by Visit
Full Analysis Set

Visit	Category	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Visit 3 (day 4)	IGA score 0 or 1	n/N* (%)	x/x (xxx)	x/x (xxx)
	IGA score 2+	n/N* (%)	x/x (xxx)	x/x (xxx)
Visit 4 (day 8)	IGA score 0 or 1	n/N* (%)	x/x (xxx)	x/x (xxx)
	IGA score 2+	n/N* (%)	x/x (xxx)	x/x (xxx)
etc.				
Visit 14 (day 85)	IGA score 0 or 1	n/N* (%)	x/x (xxx)	x/x (xxx)
	IGA score 2+	n/N* (%)	x/x (xxx)	x/x (xxx)
Visit 12 LOCF	IGA score 0 or 1	n/N* (%)	x/x (xxx)	x/x (xxx)
	IGA score 2+	n/N* (%)	x/x (xxx)	x/x (xxx)
		Cochran-Mantel-Haenzsel statistic	xx.xx	
		p-value	x.xxx	
Visit 14 LOCF	IGA score 0 or 1	n/N* (%)	x/x (xxx)	x/x (xxx)
	IGA score 2+	n/N* (%)	x/x (xxx)	x/x (xxx)
		Cochran-Mantel-Haenzsel statistic	xx.xx	
		p-value	x.xxx	

Footnote: The Cochran-Mantel-Haenszel test has been stratified by categorical baseline IGA score of (less than 4; or greater or equal to 4). Visit 12/14 LOCF was calculated as the last post baseline measurement prior to or on Visit 12/14. N is the number of subjects in the analysis set; n is the number of subjects meeting the criteria; N* is the total subjects with IGA measurement; percentages of IGA scores at each visit are calculated using n divided by N* in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming note: 1) Repeat for visits indicated in the SAP text.

Table 14.3.3.1
Proportion of Subjects who Achieved an EASI 50 Response by Visit
Full Analysis Set

Visit	Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Visit 3 (day 4)	EASI 50 responder	n/N* (%)	x/x (xxx)	x/x (xxx)
	EASI 50 non-responder	n/N* (%)	x/x (xxx)	x/x (xxx)
Visit 4 (day 8)				
etc				
Visit 12 LOCF	EASI 50 responder	n/N* (%)	x/x (xxx)	x/x (xxx)
	EASI 50 non-responder	n/N* (%)	x/x (xxx)	x/x (xxx)
Visit 14 LOCF	EASI 50 responder	n/N* (%)	x/x (xxx)	x/x (xxx)
	EASI 50 non-responder	n/N* (%)	x/x (xxx)	x/x (xxx)

Footnote: N is the number of subjects in the analysis set; n is the number of subjects meeting the criteria; N* is the total subjects with EASI measurement; Visit 12/14 LOCF was calculated as the last post baseline measurement prior to or on Visit 12/14. Percentages of EASI 50 responders and non-responders at each visit are calculated using n divided by N* in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming note: 1) Repeat for visits indicated in the SAP text.

Repeat for:

Table 14.3.3.2
Proportion of Subjects who Achieved an EASI 75 Response by Visit
Full Analysis Set

Table 14.3.3.3
Analysis of Covariance (ANCOVA) of change from baseline in EASI Score to Visit 12 LOCF
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 12 LOCF	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Adjusted LS mean [SE] (95% CI)		xx.x [xx.xx] (xx.xx, xx.xx)	xx.x [xx.xx] (xx.xx, xx.xx)
Treatment difference vs. placebo [1]: Adjusted LS mean treatment difference [SE] (95% CI)		xx.x [xx.xx] (xx.xx, xx.xx)	
p-value		x.xxx	

[1] ANCOVA model with treatment group as fixed effect and baseline EASI scoreas covariate. SE: Standard Error. CI: Confidence interval. LS: Least squares.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.3.4.1
Percent Change from Baseline in EASI Clinical Score at Each Visit
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Percent change from Baseline to Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
etc.	Max.	xx	xx
Visit 14 LOCF [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Percent change from Baseline to Visit 14 LOCF [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	Xx

Footnote: [1] Visit 12/14 LOCF was calculated as the last post baseline measurement prior to or on Visit 12/14.

Programming note: 1) Repeat for visits indicated in the SAP text.

Repeat for

Table 14.3.4.2
Percent change from Baseline in SCORAD Clinical Score at Each Visit
Full Analysis Set

Table 14.3.2.2
Percent Change from Baseline in IGA Clinical Score at Each Visit
Full Analysis Set

Table 14.3.4.4
Percent change from Baseline in Pruritus NRS Clinical Score at Each Visit
Full Analysis Set

Table 14.3.4.5
Percent change from Baseline in DLQI Clinical Score at Each Visit
Full Analysis Set

Table 14.3.5
Changes from Baseline in Transepidermal Water Loss (g/m^2/h) by Lesion/Non-Lesion Area
Full Analysis Set

Area Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Lesion area			
Baseline	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 4 (day 8)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 4 (day 8)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Repeat for Non-lesion area			

Footnote: Visit 12/14 LOCF was calculated as the last post baseline measurement prior to or on Visit 12/14.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming note: 1) Repeat for visits indicated in the SAP text.

Table 14.3.6
Anti-Drug Antibodies to GBR 830 by Visit
Full Analysis Set

Visit	Result	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Baseline (day 1)	Positive	n (%)	x (xxx)	x (xxx)
	Negative	n (%)	x (xxx)	x (xxx)
	Not done	n (%)	x (xxx)	x (xxx)
Visit 3 (day 4)	Positive	n (%)	x (xxx)	x (xxx)
	Negative	n (%)	x (xxx)	x (xxx)
	Not done	n (%)	x (xxx)	x (xxx)
etc.				
Overall [1]	Positive	n (%)	x (xxx)	x (xxx)
	Negative	n (%)	x (xxx)	x (xxx)
	Not done	n (%)	x (xxx)	x (xxx)

Footnote:

[1] If any result is positive then a subject will be counted as positive, else if any result is negative (and no result is positive) then a subject will counted as negative, else a subject will be counted as not done.

Percentages of Positive, Negative and Not Done at each visit are based on the total number of Full Analysis Set subjects in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming note: 1) Repeat for visits indicated in the SAP text.

Table 14.3.8
Changes from Baseline in Leukocytes Sub-Population Cell Counts
Full Analysis Set

Parameter Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Total T			
Baseline (day 1)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 4 (day 8)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 4 (day 8)	n	xx	Xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	Xx
	Max.	xx	Xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming note: Repeat for relevant Parameters and visits.

Repeat for (where appropriate):

Table 14.3.9
Changes from Baseline in Cellular Infiltrates
Full Analysis Set

Table 14.3.10
Changes from Baseline in Serum Total Immunoglobulin E, Serum Soluble OX40, Serum Soluble OX40 and Circulating Eosinophil Counts
Full Analysis Set

Table 14.3.12
Prohibited Medications
Full Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Study day of first prohibited medication [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Number of subjects excluded			
Visit 2	n (%)	x (xxx)	x (xxx)
Visit 3	n (%)	x (xxx)	x (xxx)
Visit 4	n (%)	x (xxx)	x (xxx)
Visit 5	n (%)	x (xxx)	x (xxx)
Visit 6	n (%)	x (xxx)	x (xxx)
Visit 7	n (%)	x (xxx)	x (xxx)
Visit 8	n (%)	x (xxx)	x (xxx)
Visit 9	n (%)	x (xxx)	x (xxx)
Visit 10	n (%)	x (xxx)	x (xxx)
Visit 11	n (%)	x (xxx)	x (xxx)
Visit 12	n (%)	x (xxx)	x (xxx)
Visit 13	n (%)	x (xxx)	x (xxx)
Visit 14	n (%)	x (xxx)	x (xxx)

Footnote: [1] Includes only prohibited medication started on or after the first dose of study drug.
Percentages are based on the total number of Full Analysis Set subjects in each treatment group. All visits on and after the first use of prohibited medication will be excluded.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.4.1
Overall Treatment Emergent Adverse Events
Safety Analysis Set

	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of subjects experiencing at least one treatment emergent event				
AE	n (%)	x (xxx)	x (xxx)	x (xxx)
Serious AE	n (%)	x (xxx)	x (xxx)	x (xxx)
AE leading to permanent withdrawal of study treatment	n (%)	x (xxx)	x (xxx)	x (xxx)
AE leading to withdrawal from study	n (%)	x (xxx)	x (xxx)	x (xxx)
AE related to investigational product	n (%)	x (xxx)	x (xxx)	x (xxx)
AE leading to death	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: Percentages are based on the total number of Safety Analysis Set subjects in each treatment group. Subjects are counted only once per reason. Only events beginning or worsening after the first dose of study drug are included in this output.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.4.2.1
Treatment Emergent Adverse Events
Safety Analysis Set

System Organ Class Preferred Term	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of subjects with any treatment emergent AE	n (%)	x (xxx)	x (xxx)	x (xxx)
System Organ Class 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 2	n (%)	x (xxx)	x (xxx)	x (xxx)
System Organ Class 2	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 2	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: At each level of summarization a subject is counted once if the subject reported one or more events in a given level of summarization.
Percentages are based on the total number of Safety Analysis Set subjects in each treatment group. Preferred terms within the organ classes are sorted in descending order by the overall column. Only events beginning or worsening after the first dose of study drug are included in the summaries. Adverse event terms are coded using MedDRA version 19.0.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Table 14.4.2.2
Serious Treatment Emergent Adverse Events
Safety Analysis Set

Table 14.4.2.5
Treatment Emergent Adverse Events Leading to Discontinuation of Study
Safety Analysis Set

Table 14.4.2.6
Treatment Emergent Adverse Events Related to the Investigational Product
Safety Analysis Set

Table 14.4.2.7
Treatment Emergent Adverse Events Leading to Death
Safety Analysis Set

Table 14.4.2.8
Treatment Emergent Adverse Events by Severity
Safety Analysis Set

Severity **System Organ Class** **Preferred Term**	**Statistic**	**GBR 830 (N=xx)**	**Placebo (N=xx)**	**Overall (N=xx)**
Number of subjects with any treatment emergent AE	n (%)	x (xxx)	x (xxx)	x (xxx)
Severe	n (%)	x (xxx)	x (xxx)	x (xxx)
Moderate	n (%)	x (xxx)	x (xxx)	x (xxx)
Mild	n (%)	x (xxx)	x (xxx)	x (xxx)
Severe				
System Organ Class 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 2	n (%)	x (xxx)	x (xxx)	x (xxx)
System Organ Class 2	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred Term 2	n (%)	x (xxx)	x (xxx)	x (xxx)

Footnote: At each level of summarization a subject is counted once if the subject reported one or more events in a given level of summarization. Subjects with multiple severities will be counted under their most severe category. If severity is missing subject will be considered in the severe category. Preferred terms within the organ classes under severity level are sorted in descending order by the overall column. Only events beginning or worsening after the first dose of study drug are included in the summaries. Percentages are based on the total number of Safety Analysis Set subjects in each treatment group. Adverse event terms are coded using MedDRA version 19.0.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.4.3
Study Drug Treatment Compliance
Safety Analysis Set

Parameter	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Total % compliance to study treatment [1]	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Number of subjects above 80% compliance	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 2				
Number of subjects who completed 1 hour infusion of study drug	n (%)	x (xxx)	x (xxx)	x (xxx)
% compliance to study drug	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Visit 7 …				

Footnote: [1] Total compliance is calculated as: (Visit 2 actual volume administered + Visit 7 actual volume administered) / (Visit 2 planned volume to be administered + Visit 7 planned volume to be administered) x 100. Percentages are based on the total number of subjects in Safety Analysis Set in each treatment group.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Table 14.4.4.1
Concomitant Medications for Atopic Dermatitis and Related Conditions
Safety Analysis Set

ATC Level 1 **ATC Level 2** **ATC Level 3** **ATC Level 4** **Preferred Term**	**Statistic**	**GBR 830 (N=xx)**	**Placebo (N=xx)**	**Overall (N=xx)**
ATC Level 1				
ATC Level 2				
ATC Level 3				
ATC Level 4				
Preferred term 1	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 2	n (%)	x (xxx)	x (xxx)	x (xxx)
Preferred term 3	n (%)	x (xxx)	x (xxx)	x (xxx)
Etc				

Footnote: Percentages are based on the total number of subjects in Safety Analysis Set in each treatment group. Preferred terms within the ATC level are sorted in descending order by the overall column Medications were coded using WHO DDE (Sep 2015).

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Table 14.4.4.2
Concomitant Non-Drug Treatments
Safety Analysis Set

Table 14.4.4.3
Rescue Medications
Safety Analysis Set

Programming note: concomitant rescue meds only will be summarized.

Table 14.4.5.1
Change from Baseline in Laboratory Results by Category, Parameter and Visit
Safety Analysis Set

Laboratory Category: Haematology

Parameter Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Haemoglobin (unit)			
Baseline	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Footnote: Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes: Repeat for the categories, parameters and relevant visits indicated in the SAP. Also include final assessment visit and change from baseline. Do not present day 1 on the baseline label.

Table 14.4.5.2
Shift Table of Laboratory Results from Baseline to Worst Post Baseline Result by Category and Treatment Group
Safety Analysis Set

Laboratory Category: Haematology
Treatment: GBR 830

Parameter	Worst Post-Baseline Result	Statistic	Baseline				
			Abnormal, low	Normal	Abnormal, high	Missing	Total
Haemoglobin (unit)							
	Abnormal, low	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Normal	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Abnormal, high	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Missing	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Total	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
Etc.							

Footnote: N* is the number of subjects with the result at the Baseline visit. Percentages are based on N* in each treatment group. Baseline is the last recorded value for each parameter prior to treatment. If a subject has both an 'abnormal, low' and an 'abnormal, high' worst post baseline result, both results will be included.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes: Repeat for the categories and parameters indicated in the SAP. If required add 'Abnormal, (low and high)' column and row to the output for all parameters.

Table 14.4.6.1
Change from Baseline in Vital Signs Results by Parameter and Visit
Safety Analysis Set

Parameter Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Systolic blood pressure (mmHg)			
Baseline	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Footnote: Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming note: repeat for appropriate visits and parameters- Diastolic blood pressure (mmHg), body temperature (°C), pulse rate (bpm), weight (kg), bmi (kg/m^2) Do not present day 1 on the baseline label.

Table 14.4.6.2
Shift Table of Vital Signs from Baseline to Worst Post Baseline Result by Treatment Group
Safety Analysis Set

Treatment: GBR 830

Parameter Visit	Worst Post-baseline Result	Statistic	Baseline				
			Normal	Abnormal (NCS)	Abnormal (CS)	Missing	Total
Systolic blood pressure (mmHg)							
	Normal	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Abnormal (NCS)	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Abnormal (CS)	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Missing	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Total	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
Diastolic blood pressure (mmHg)							
	Normal	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Abnormal (NCS)	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Abnormal (CS)	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Missing	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)
	Total	n/N* (%)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)	x/X (xxx)

Footnote: N* is the number of subjects with the result at the Baseline visit. Percentages are based on N* in each treatment group. NCS: Not Clinically Significant. CS: Clinically significant. Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017

Programming note: repeat for appropriate visits and parameters- Diastolic blood pressure (mmHg), body temperature (°C), pulse rate (bpm), weight (kg), BMI (kg/m^2)

Table 14.4.7
Physical Examination Results
Safety Analysis Set

Parameter Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Thorax/Lungs				
Baseline				
Done	n (%)	x (xxx)	x (xxx)	x (xxx)
Not done	n (%)	x (xxx)	x (xxx)	x (xxx)
Worst post-baseline				
Not examined	n (%)	x (xxx)	x (xxx)	x (xxx)
Normal	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal, not clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal, clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Etc.				

Footnote: Percentages are based on the total number of subjects in Safety Analysis Set in each treatment group. Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for Parameters: Cardiovascular system, Neurological examination, Other.

Table 14.4.8.1
Change from Baseline in Electrocardiogram Results by Parameter and Visit
Safety Analysis Set

Parameter Visit	Statistic	GBR 830 (N=xx)	Placebo (N=xx)
Heart rate (bpm)			
Baseline	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline to Visit 3 (day 4)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Footnote: Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming Notes:
1. Include all 12-lead ECG data listed in the protocol: PR interval (ms), RR interval (ms), QRS duration (ms), QT interval (ms), QTcF interval (ms) , repeat for relevant visits.

Table 14.4.8.2
Overall Interpretations of Electrocardiogram by Visit
Safety Analysis Set

Visit Categorization	Statistic	GBR 830 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Overall prolongation				
QTc interval > 500ms at any visit	n (%)	x (xxx)	x (xxx)	x (xxx)
QTc interval > 60ms change at any post baseline visit	n (%)	x (xxx)	x (xxx)	x (xxx)
Baseline				
Normal	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal not clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal and clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 3 (day 4)				
Normal	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal not clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal and clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Visit 4 (day 8)				
Normal	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal not clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
Abnormal and clinically significant	n (%)	x (xxx)	x (xxx)	x (xxx)
…etc.				

Footnote: Percentages are based on the total number of subjects in Safety Analysis Set in each treatment group. Baseline is the last recorded value for each parameter prior to treatment.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Programming notes: repeat for relevant planned visits.

Table 14.4.9
GBR830 Serum Concentration (ng/mL) Data by Dose Interval
Pharmacokinetic Analysis Set

LLOQ=xx.xx ng/mL

Dose Interval Time Point	n	Mean	SD	CV (%)	Median	Min	Max
Dose 1							
pre dose (-0.25 hours)	xx	xx.x	xx.xx	xx.xx	xx.x	xx	xx
end of dose (1 hours)	xx	xx.x	xx.xx	xx.xx	xx.x	xx	xx
post dose (1.5 hours)	xx	xx.x	xx.xx	xx.xx	xx.x	xx	xx
Etc.							

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y
Programming note: repeat for all time points and dose 2 – see SAP text for dose interval details.

Table 14.4.10
Pharmacokinetic Parameters of GBR830 by Dose Interval
Pharmacokinetic Analysis Set

Dose Interval	Statistic	AUC0-t (µg.h/mL)	AUC0-tau (µg.h/mL)	AUC0-∞ (µg.h/mL)	Cmax (µg/mL)	Tmax (h)	λz (1/h)	t1/2 (h)	Vd (L)	CL (L/h)
Dose 1	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	CV (%)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Max.	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Geometric CV (%)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Footnote: AUC0-∞=area under the (serum) concentration-time curve to infinity; AUC0-t=area under the (serum) concentration-time curve to the last time point where quantifiable concentration is observed; AUC0-tau=area under the (serum) concentration-time curve to the last observed time point in the interval; CL=clearance; Cmax=maximum concentration; Tmax=Time of Cmax. t1/2=terminal half-life; Vd=volume of distribution.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming note: repeat for dose 2.

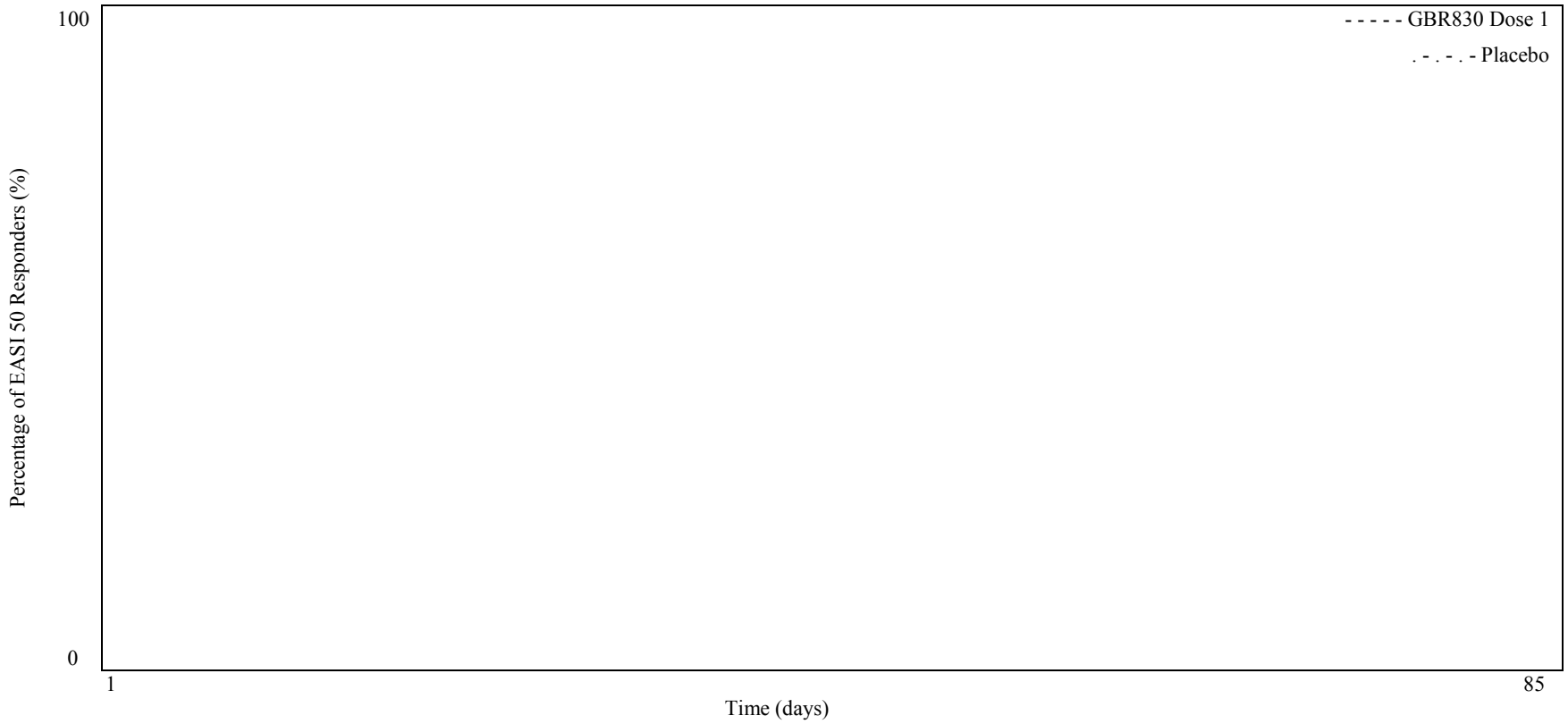
Figure 14.3.1.1
Box plot of biomarker CCL11/hARPby Planned Treatment Group
Biological Activity Set

Footnote: Source table: 14.3.1.1

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for: Figure 14.3.1.2 to 14.3.1.19 biomarkers as appropriate.

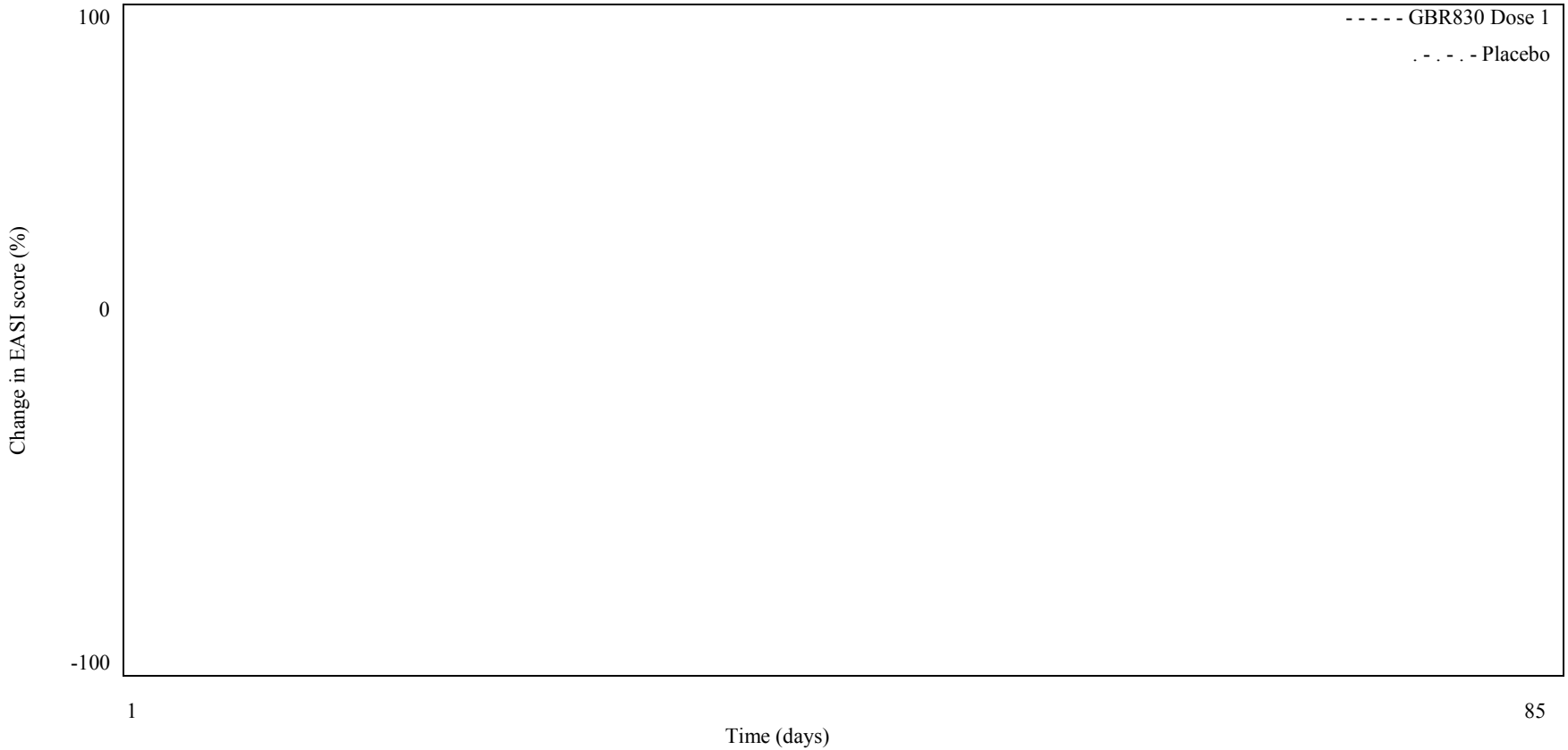
Figure 14.3.3.1
Line Plot of EASI 50 Responders over Time (days) by Planned Treatment Group
Full Analysis Set



Footnote: Source table: 14.3.3.1.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Figure 14.3.4.1
Line Plot of Mean ± SE Percentage Change in EASI Score over Time (days) by Planned Treatment Group
Full Analysis Set



Footnote: Source table: 14.3.4.1.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Figure 14.3.4.4
Line Plot of Mean ± SE Percentage Change in Pruritus NRS over Time (days) by Planned Treatment Group
Full Analysis Set

Footnote: Source table: 14.3.4.4.

Figure 14.3.6.1
Scatter Plot of Serum Concentration (µg/mL) over Anti Drug Antibody Status by Planned Treatment Group
Pharmacokinetic Analysis Set

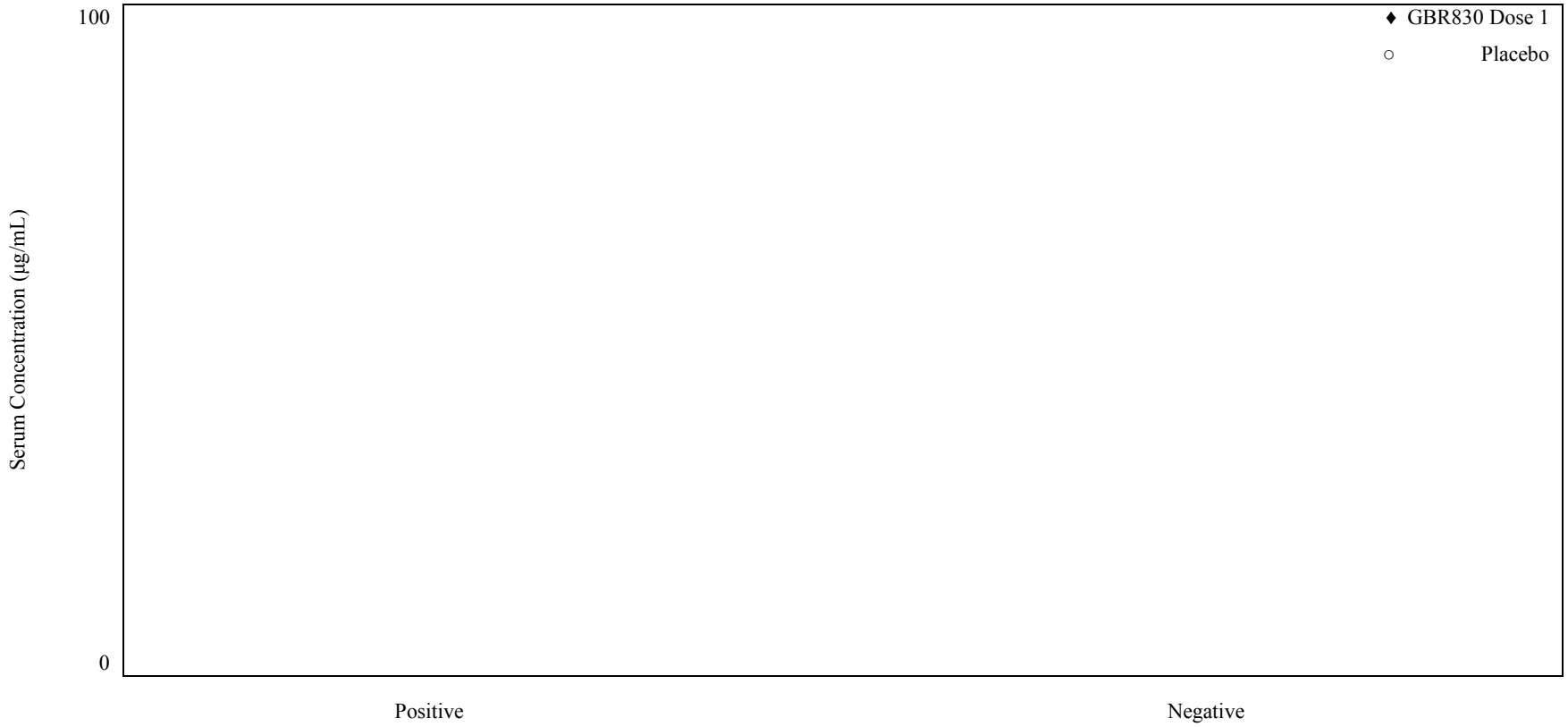
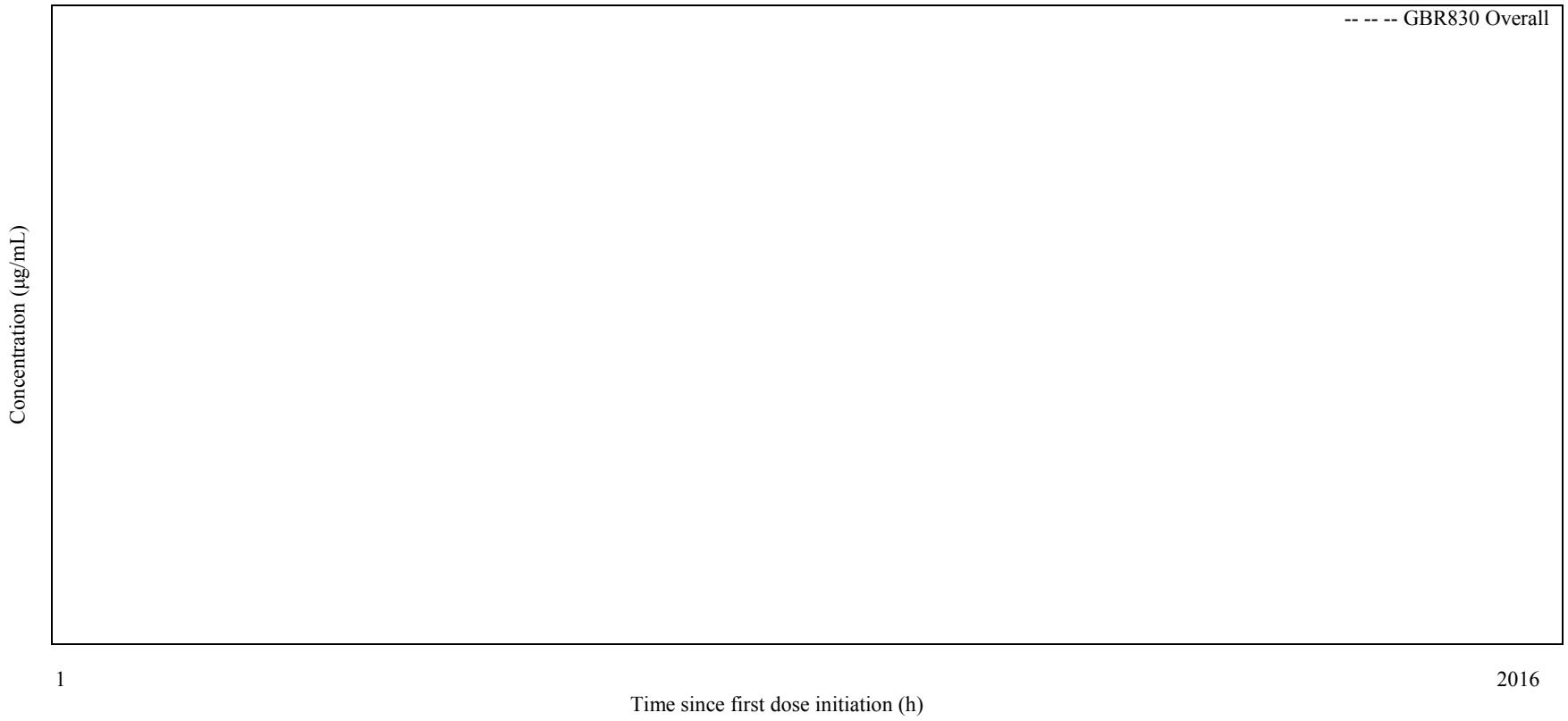


Figure 14.4.11.1
Mean Serum GBR830 Concentration Data (0 to 2016 hours) Overall
Pharmacokinetic Analysis Set

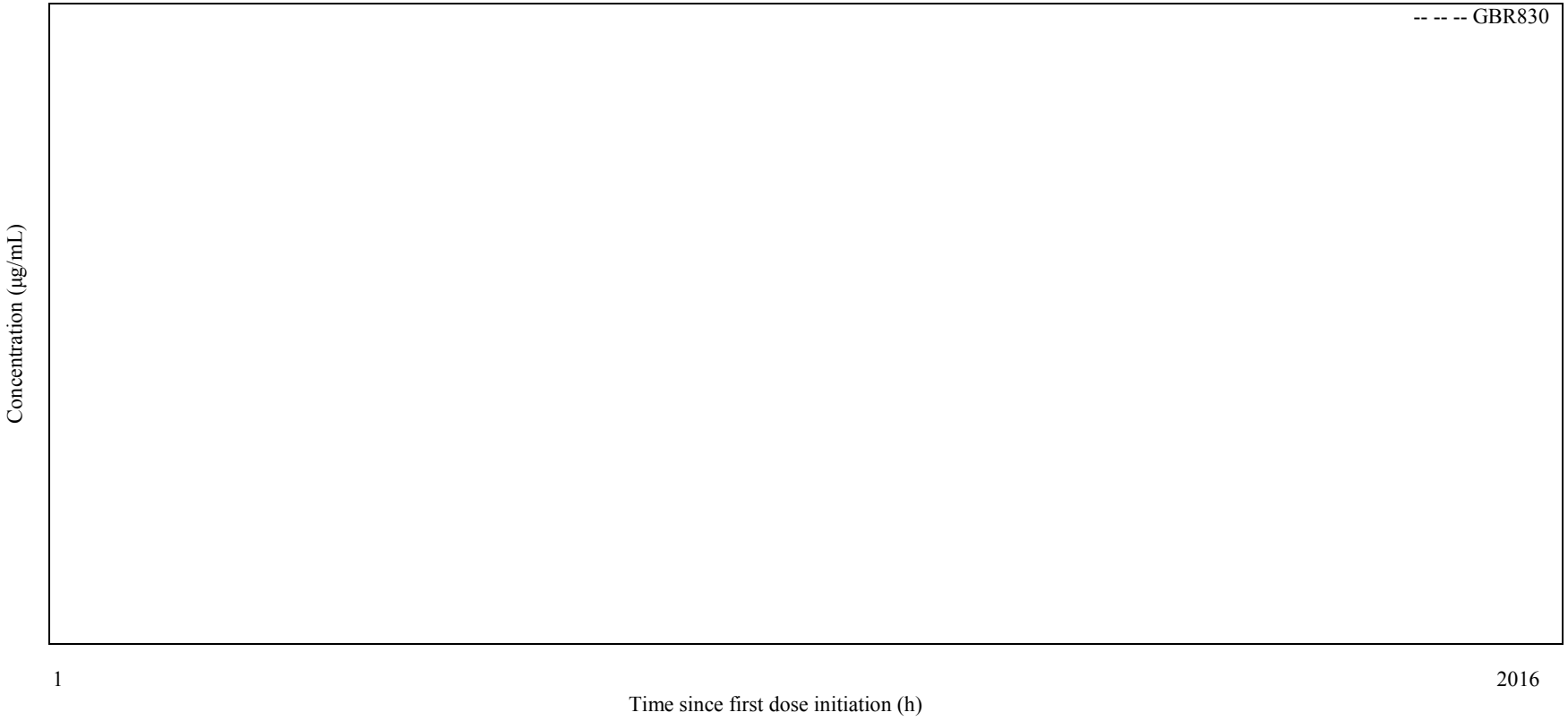
N= XX



SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Figure 14.4.11.2
Individual Subject Profiles of Serum GBR830 Concentration Data (0 to 2016 hours)
Pharmacokinetic Analysis Set

Subject ID: XXX-XXXX



SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Listing 16.1.1
Subject Disposition
Randomized Subjects

Planned Treatment	Subject ID	Date of First Treatment	Date of Last Treatment	Date of Withdrawal from Study	Study Day of Withdrawal	Did Subject Complete all Scheduled Visits?	Reason for Withdrawal
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	Yes	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	x	xxx	xxxxxxxxxx

Footnote: If status is ‘Lost to Follow up’ Reason for withdrawal will include the date of last contact with subject. If Subject status is ‘Death’, date of death will be included.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Listing 16.1.2
Analysis Populations
Screened Subjects

Subject ID	Screened	Randomized	Full Analysis Set	Safety Analysis Set	Pharmacokinetic Analysis Set	Biological Activity Set
xx-xxxxxx	Yes	Yes	Yes	Yes	Yes	Yes
xx-xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx
xx-xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.1.3
Subject Inclusion/Exclusion Criteria
Screened Subjects

Planned Treatment	Subject ID	Visit	Inclusion Criteria met?	Reason Inclusion Criteria not met	Exclusion criteria met?	Reason Exclusion criteria not met	Randomization status
	xx-xxxxxx	Screening	No	xxxxxxxxxxxxxxxx	Yes		Screen Failed
	xx-xxxxxx	Screening	Yes		Yes		
		Baseline	Yes		No	xxxxxxxxxxxxxxxx	Screen Failed
	xx-xxxxxx	Screening	Yes		Yes		
xxx	xx-xxxxxx	Baseline	Yes		Yes		Randomized

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Listing 16.1.4
Screen Failure Subjects
Screened Subjects

Subject ID	Reason for Screen Failure	Rescreened	Replaced	Previous Screening Number
xx-xxxxxx	Xxxxxxxxxxxxxxxxxxxxxxxxxxxx	Yes	No	xx-xxxxxx
xx-xxxxxx	Xxxxxxxxxxxxxxxxxxxxxxxxxxxx	Yes	No	xx-xxxxxx
xx-xxxxxx	Xxxxxxxxxxxxxxxxxxxxxxxxxxxx	No	Yes	

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.1.5
Subject Randomization Information
Randomized Subjects

Planned Treatment	Subject ID	Date of Consent	Date of Randomization	Randomization number	Blind Broken?	Date Blind Broken	Reason for Blind Broken
GBR 830	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	Yes	DDMMMYYYY	xxxxxxxxxxxxxxx
Placebo	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	No		
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	xxx		
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	xxx		
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	xxx		
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	xxx		
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxxx	xxx		

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.1.1.1
Subject Demographic and Baseline Characteristics – Part 1
Randomized Subjects

Planned Treatment	Subject ID	Date of Birth (Age)	Sex	Race	Weight (kg)	Height (cm)	Body Mass Index (kg/m^2)	Body Surface Area (m^2)
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	Male	Asian	xx.x	xx.x	xxx	Xxx
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	Female	xxxxxxxx	xx.x	xx.x	xxx	Xxx
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	xxxx	xxxxxxxx	xx.x	xx.x	xxx	Xxx
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	xxxx	xxxxxxxx	xx.x	xx.x	xxx	Xxx
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	xxxx	xxxxxxxx	xx.x	xx.x	xxx	Xxx
xxxxxxxx	xx-xxxxxx	DDMMMYYYY (xx)	xxxx	xxxxxxxx	xx.x	xx.x	xxx	Xxx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.2.1.1.2
Subject Demographic and Baseline Characteristics – Part 1
Screen Failure Subjects

Listing 16.2.1.2.1
Subject Demographic and Baseline Characteristics – Part 2
Randomized Subjects

Planned Treatment	Subject ID	Age at AD diagnosis	Ethnicity	Country	Child Bearing Potential, Specify	Duration of Non Child Bearing Potential
xxxxxxxx	xx-xxxxxx	xx	Hispanic or Latino	Canada	N/A	
xxxxxxxx	xx-xxxxxx	xx	Not Hispanic or Latino	xxxxxxxx	No, Post menopausal	> 1 year
xxxxxxxx	xx-xxxxxx	xx	xxxx	xxxxxxxx		
xxxxxxxx	xx-xxxxxx	xx	xxxx	xxxxxxxx		
xxxxxxxx	xx-xxxxxx	xx	xxxx	xxxxxxxx		
xxxxxxxx	xx-xxxxxx	xx	xxxx	xxxxxxxx		

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.2.1.2.2
Subject Demographic and Baseline Characteristics – Part 2
Screen Failure Subjects

Listing 16.2.2
Atopic Dermatitis History
Randomized Subjects

Planned Treatment	Subject ID	Years since AD diagnosis	Type of AD	Any History of Allergy?	Was Patch Test Performed?	Any Known Allergen identified?	Concomitant Atopic Illness	Remarks	Result of Skin Biopsy performed in Past?	Any treatment administered for AD or associated conditions?
xxxxxxx	xxx-xxxxx	xx	Intrinsic	Yes	Yes	xxxxxxxxxxxx	Asthma		Eosinophilic	Yes
xxxxxxx	xxx-xxxxx	xx	Extrinsic	No	No		Asthma, Skin Conditions		Non-eosinophilic	No
xxxxxxx	xxx-xxxxx	xx	Intrinsic	No	No		Asthma, Other , xxxxxx	xxxxxxxxx	Other , xxxxxx	
							None		Not done	

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.3
Medical/Surgical History
Randomized Subjects

Planned Treatment	Subject ID	Start Date	End date	Ongoing?	Body System	Condition/Procedure	Severity grade
xxxxxxx	xx-xxxxxx	DDMMMYYYY		Yes	HEENT	xxxxxxxxxxx	Mild
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	No	xxxxxxxx	xxxxxxxxxxx	Moderate
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxx	xxxxxxxx	xxxxxxxxxxx	Severe
xxxxxxx	xx-xxxxxx	DDMMMYYYY	DDMMMYYYY	xxx	xxxxxxxx	xxxxxxxxxxx	Not Known

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.4.1
Smoking, Alcohol and Drug Abuse History – Part 1
Randomized Subjects

Planned Treatment	Subject ID	Alcohol User?	Alcohol Stop Date	Alcohol Consumption (ml/Week)	Is There History of Alcohol Abuse?	Drug Abuse?	Drug Abuse Stop Date	Form of Drug	Clinically Significant?
xxxxxxx	xxx-xxxxx	Former	DDMMMYYYY	xxxx.xx	Yes	Former	DDMMMYYYY	xxxxxxx	Yes
xxxxxxx	xxx-xxxxx	Current		xxxx.xx	No	Current			No
xxxxxxx	xxx-xxxxx	N/A		N/A	No	N/A			

Footnote: Clinical significance of drug use is determined by the opinion of the investigator or if the subject meets the DSM-V criteria for abuse.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.4.2
Smoking, Alcohol and Drug Abuse History – Part 2
Randomized Subjects

Planned Treatment	Subject ID	Smoker?	Smoking Stop Date	Number of Cigarettes per day	Smokeless Tobacco User?	Tobacco Consumption Stop Date	Form of Tobacco
xxxxxxx	xxx-xxxxx	Former	DDMMMYYYY	xxx	Former	DDMMMYYYY	xxxxxxxxxxxx
xxxxxxx	xxx-xxxxx	Current		xxx	Current		
xxxxxxx	xxx-xxxxx	N/A		N/A	N/A		

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.2.5.1
Atopic Dermatitis and Related Conditions Baseline Prior Medications
Randomized Subjects

Planned Treatment	Subject ID	ATC Level/ Preferred Term/ Verbatim Term	Start Date	Stop Date	Ongoing at Baseline	Dose (Unit)	Route/Frequency	Indication
xxxxxxx	xxx-xxxxx	Xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxx	DDMMMYYYY		Yes	xxx (xxx)	PO/OD	xxxxxxx
		Xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxx	DDMMMYYYY	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
		Xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxx	DDMMMYYYY	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
		Xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxx	DDMMMYYYY	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
xxxxx	xxx-xxxxxx	Xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxx	…					

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.2.5.2
Other Baseline Prior Medications
Randomized Subjects

Listing 16.2.6
Baseline Physical Examination
Randomized Subjects

Planned Treatment	Subject ID	Physical Examination Performed?	Body System	Results	Comments
xxxxx	xxx-xxxxxx	Done	Neck	Normal	
			HEENT	Abnormal CS	xxxx
			Skin	Not Examined	xxxx
xxxxx	xxx-xxxxxx	Not Done			

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.3.1
Active AD mRNA Expression Signature and Pathologic Epidermal Phenotype Measures
Full Analysis Set

Planned Treatment	Subject ID	Parameter	Visit (Study Day)*	Visit Date	Measurement	Measurement Change From Baseline
xxxxxxx	xx-xxxxxx	hARP	2 (1)*	DDMMMYYYY	xxx.xx	N/A
			7 (29)	DDMMMYYYY	xxx.xx	xxx.xx
			Unscheduled (31)	DDMMMYYYY	xxx.xx	xxx.xx
			13 (71)	DDMMMYYYY	xxx.xx	xxx.xx
		K16	2 (1)*	DDMMMYYYY	xxx.xx	N/A
			7 (29)	DDMMMYYYY	xxx.xx	xxx.xx
			13 (71)	DDMMMYYYY	xxx.xx	xxx.xx
	etc.					
xxxxxxx	xx-xxxxxx	hARP	2 (1)*	DDMMMYYYY	xxx.xx	N/A
			7 (29)	DDMMMYYYY	xxx.xx	xxx.xx
			13 (71)	DDMMMYYYY	xxx.xx	xxx.xx
		K16	2 (1)*	DDMMMYYYY	xxx.xx	N/A
			7 (29)	DDMMMYYYY	xxx.xx	xxx.xx
			13 (71)	DDMMMYYYY	xxx.xx	xxx.xx

Footnote: * indicates the baseline record.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming notes: 1) Repeat for parameters mRNA in primary analysis table

Listing 16.3.2
IGA Scores
Full Analysis Set

Planned Treatment	Subject ID	Visit (Study Day)*	Visit Date	IGA Score#	Score Category
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	0	0 or 1
		3 (4)	DDMMMYYYY	3	2 +
		4 (8)	DDMMMYYYY	3	2 +
		5 (15)	DDMMMYYYY	3	2 +
		6 (22)	DDMMMYYYY		2 +
		7 (29)	DDMMMYYYY	4	2 +
		8 (32)	DDMMMYYYY	xx	xx
		9 (36)	DDMMMYYYY	xx	xx
		10 (43)	DDMMMYYYY	xx	xx
		11 (50)	DDMMMYYYY	xx	xx
		12 (57)	DDMMMYYYY	xx	xx
		13 (71)	DDMMMYYYY	xx#	xx
		14 (85)	DDMMMYYYY	xx#	xx

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.3.3
EASI Scores
Randomized Subjects

Planned Treatment	Subject ID	Visit (Study Day)*	Visit Date	EASI score #	EASI 50 responder?	EASI 75 responder?	Percent change from Baseline
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	60	N/A	N/A	N/A
		3 (4)	DDMMMYYYY	15	Yes	Yes	xx
		4 (8)	DDMMMYYYY		No	No	xx
		5 (15)	DDMMMYYYY	xxx	xxx	Xxx	xx
		6 (22)	DDMMMYYYY	xxx	xxx	Xxx	xx
		7 (29)	DDMMMYYYY	xxx	xxx	Xxx	xx
		8 (32)	DDMMMYYYY	xxx	xxx	Xxx	xx
		9 (36)	DDMMMYYYY	xxx	xxx	Xxx	xx
		10 (43)	DDMMMYYYY	xxx	xxx	Xxx	xx
		11 (50)	DDMMMYYYY	xxx	xxx	Xxx	xx
		12 (57)	DDMMMYYYY	xxx	xxx	Xxx	xx
		13 (71)	DDMMMYYYY	xxx	xxx	Xxx	xx
		14 (85)	DDMMMYYYY	xxx	xxx	Xxx	xx

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.3.4.1
SCORAD Clinical Scores
Full Analysis Set

Planned Treatment	Subject ID	Visit (Study Day)*	Visit Date	Measurement#	Measurement Change from Baseline	Percent change from Baseline
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	xx	N/A	N/A
		3 (4)	DDMMMYYYY	xx	xx	xx
		4 (8)	DDMMMYYYY	xx	xx	xx
		5 (15)	DDMMMYYYY	xx	xx	xx
		6 (22)	DDMMMYYYY	xx	xx	xx
		7 (29)	DDMMMYYYY	xx	xx	xx
		8 (32)	DDMMMYYYY	xx	xx	xx
		9 (36)	DDMMMYYYY	xx	xx	xx
		10 (43)	DDMMMYYYY	xx	xx	xx
		11 (50)	DDMMMYYYY	xx	xx	xx
		12 (57)	DDMMMYYYY	xx	xx	xx
		13 (71)	DDMMMYYYY	xx	xx	xx
		14 (85)	DDMMMYYYY	xx	xx	xx

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.3.4.4
Pruritus NRS Clinical Scores
Full Analysis Set

Listing 16.3.4.5
DLQI Clinical Scores
Full Analysis Set

Listing 16.3.5
Transepidermal Water Loss Readings
Full Analysis Set

Planned Treatment	Subject ID	Area	Visit (Study Day)*	Visit Date	Measurement#	Measurement change from baseline
xxxxxxx	xx-xxxxxx	Lesion	2 (1)*	DDMMMYYYY	xxx.xx	N/A
			3 (4)	DDMMMYYYY	xxx.xx	xxx.xx
			4 (8)	DDMMMYYYY	xxx.xx	xxx.xx
			5 (15)	DDMMMYYYY	xxx.xx	xxx.xx
			6 (22)	DDMMMYYYY	xxx.xx	xxx.xx
			7 (29)	DDMMMYYYY	xxx.xx	xxx.xx
			8 (32)	DDMMMYYYY	xxx.xx	xxx.xx
			9 (36)	DDMMMYYYY	xxx.xx	xxx.xx
			10 (43)	DDMMMYYYY	xxx.xx	xxx.xx
			11 (50)	DDMMMYYYY	xxx.xx	xxx.xx
			12 (57)	DDMMMYYYY	xxx.xx	xxx.xx
			13 (71)	DDMMMYYYY	xxx.xx	xxx.xx
			14 (85)	DDMMMYYYY	xxx.xx	xxx.xx
		Non-Lesion	2 (1)*	DDMMMYYYY	xxx.xx	N/A
	etc.					

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.3.6
Anti-Drug Antibodies (ADA)
Safety Analysis Set

Actual Treatment	Subject ID	Visit (Study Day)*	Visit Date	Titration#	Antibody	Neutralizing Antibody
xxxxxxx	xx-xxxxxx	2 (1)*	DDMMMYYYY	xxx	Negative	
		5 (15)	DDMMMYYYY	xxx	Negative	
		7 (29)	DDMMMYYYY	xxx	Positive	
		12 (57)	DDMMMYYYY		Negative	
		14 (85)	DDMMMYYYY	xxx	Negative	

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.3.8
Leukocytes Sub-Population Cell Counts
Full Analysis Set

Planned Treatment	Subject ID	Parameter	Visit (Study Day)*	Visit Date	Measurement#	Measurement Change from Baseline	Percent change from Baseline
xxxxxxx	xx-xxxxxx	XXX	2 (1)*	DDMMMYYYY	xx	N/A	N/A
			7 (29)	DDMMMYYYY	xx	xx	xx
			13 (71)	DDMMMYYYY	xx#	xx	xx

Footnote: * indicates the baseline record. # indicates measures that were excluded following a prohibited medication.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM

Repeat for:

Listing 16.3.9
Cellular Infiltrates
Full Analysis Set

Listing 16.3.10
Serum Total Immunoglobulin E, Serum Soluble OX40, Serum Soluble OX40 and Circulating Eosinophil Counts
Full Analysis Set

Listing 16.3.12
Prohibited Medications
Full Analysis Set

Actual Treatment	Subject ID	Prohibited Medication	Date of Prohibited Medication	Study Day
xxxxxxx	xx-xxxxxx	xxxxxxxxx	DDMMMYYYY	xx
		xxxxxxxxx	DDMMMYYYY	xx
		xxxxxxxxx	DDMMMYYYY	xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.4.1.1.1
Adverse Events – Part 1
Safety Analysis Set

Actual Treatment	Subject ID	AE No.	Age	Sex	System Organ Class (Preferred Term) [Verbatim Term]	Start Date/Time (Study Day)	Stop Date/Time (Study Day)	Time on Treatment at Onset of Event (Days)	Duration of AE (days)	SAE
xxxxxxx	xx-xxxxxx	1	xx	xx	XXXXXXXXXXXXXXXXXXXX (XXXXXXXXXXXXXXX) [XXXXXXXXXXXXXXX]	DDMMMYYYY/ HH:MM (xxx)	DDMMMYYYY/ HH:MM (xxx)	xx	xx	Y
		2	xx	xx	XXXXXXXXXXXXXXXXXXXX (XXXXXXXXXXXXXXX) [XXXXXXXXXXXXXXX]	DDMMMYYYY/ HH:MM (xxx)	DDMMMYYYY/ HH:MM (xxx)	xx	xx	
		3	xxxx	xxxx	XXXXXXXXXXXXXXXXXXXX (XXXXXXXXXXXXXXX) [XXXXXXXXXXXXXXX]	DDMMMYYYY/ HH:MM (xxx)	DDMMMYYYY/ HH:MM (xxx)	xx	xx	

Footnote:. SAE: Serious Adverse Event.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.4.1.2.1
Serious Adverse Events – Part 1
Safety Analysis Set

Listing 16.4.1.5.1
Adverse Events Leading to Discontinuation of Study – Part 1
Safety Analysis Set

Listing 16.4.1.7.1
Adverse Events Leading to Death – Part 1
Safety Analysis Set

Listing 16.4.1.1.2
Adverse Events – Part 2
Safety Analysis Set

Actual Treatment	Subject ID	AE No.	Severity	Relationship to Study Treatment	Action Taken with Study Treatment	Other Action Taken	Outcome	Treatment Emergent Flag
xxxxxxx	xx-xxxxxx	1	Mild	Related	Permanently withdrawn	Concomitant Medication given	Improved	Y
		2	Moderate	Not Related	xx	xx	xx	N
		3	Xxxx	xxxx	xx	xx	xx	

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.4.1.2.2
Serious Adverse Events – Part 2
Safety Analysis Set
Include SAE criteria detail

Listing 16.4.1.5.2
Adverse Events Leading to Discontinuation of Study – Part 2
Safety Analysis Set

Listing 16.4.1.7.2
Adverse Events Leading to Death – Part 2
Safety Analysis Set

Listing 16.4.2
Study Drug Administration
Safety Analysis Set

Actual Treatment	Subject ID	Visit (Study Day)	Dosing Date	Start time	End time	Total Volume Prepared (mL)	Planned Volume to be Administered (mL)	Actual Volume Administered (mL)	Compliance (%)
xxxxxxx	xx-xxxxxx	2 (1)	DDMMMYYYY	HH:MM	HH:MM	xx.xx	xx.xx	xx.xx	xx.xx
		7 (29)	DDMMMYYYY	HH:MM	HH:MM	xx.xx	xx.xx	xx.xx	xx.xx
		Overall				xx.xx	xx.xx	xx.xx	xx.xx
xxxxxxx	xx-xxxxxx	2 (1)	DDMMMYYYY	HH:MM	HH:MM	xx.xx	xx.xx	xx.xx	xx.xx
		7 (29)	DDMMMYYYY	HH:MM	HH:MM	xx.xx	xx.xx	xx.xx	xx.xx
		Overall				xx.xx	xx.xx	xx.xx	xx.xx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.4.3.1
Concomitant Medications
Safety Analysis Set

Actual Treatment	Subject ID	ATC Level/ Preferred Term/ Verbatim Term	Start Date (Study Day)[1]	Stop Date	Ongoing?	Dose (Unit)	Route/Frequency	Indication
xxxxxxx	xxx-xxxxx	Xxxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxxx/ xxxxxxxxxxxxx	DDMMMYYYY (xx)		Yes	xxx (xxx)	PO/OD	xxxxxxx
		Xxxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxxx/ xxxxxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
		Xxxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxxx/ xxxxxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
		Xxxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxxx/ xxxxxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxx (xxx)	xxx	xxxxxxx
xxxxx	xxx-xxxxxx	Xxxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxxx/ xxxxxxxxxxxxx	…					

1. **Footnote**: [1] medications that started prior to Baseline will have 'NA' as the study day. Medications have been coded using WHO DDE (Sep 2015).

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Repeat for:

Listing 16.4.3.3
Rescue Medications
Safety Analysis Set

Listing 16.4.3.2
Concomitant Non-Drug Therapies
Safety Analysis Set

Actual Treatment	Subject ID	Non-Drug Treatment	Start Date (Study Day)	Stop Date	Ongoing?	Reason
xxxxxxx	xxx-xxxxx	xxxxxxxxx	DDMMMYYYY (xx)		Yes	xxxxxxxxxxxxx
		xxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxxxxxxxxxxxx
		xxxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxxxxxxxxxxxx
		xxxxxxxxxxxxxx	DDMMMYYYY (xx)	DDMMMYYYY	xxx	xxxxxxxxxxxxx
xxxxx	xxx-xxxxxx	xxxxxxxxxx	…			

1. **Footnote**: Medications that started prior to Baseline will have 'NA' as the study day. Medications have been coded using WHO DDE (Sep 2015).

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.4.4.1.1
Heamatology Results
Safety Analysis Set

Actual Treatment	Subject ID	Age/Sex	Laboratory Parameter (unit)	Visit (Study Day)	Date/Time of collection	Result	Normal Range	Comment
xxxxxxx	xxx-xxxxx	xx/Male	xxxxxxxxxx (xx)	2 (1)	DDMMMYYYY/ MM:HH	xxx (H)	xx – xx	xxxxxxxxx
				3 (4)	DDMMMYYYY/ MM:HH	xxx (L)	xx – xx	xxxxxxxxx
				4 (8)	DDMMMYYYY/ MM:HH	xxx	xx – xx	xxxxxxxxx
				U (26)				
	etc.							

Footnote: H = result above normal range; L = result below normal range; U = unscheduled visit.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Repeat for:

Listing 16.4.4.1.2
Subjects with Abnormal Hematology Results
Safety Analysis Set

Listing 16.4.4.2.1
Serum Biochemistry Results
Safety Analysis Set

Listing 16.4.4.2.2
Subjects with Abnormal Serum Biochemistry Results
Safety Analysis Set

Listing 16.4.4.3
Urinalysis Results
Safety Analysis Set

Listing 16.4.4.4
Serology Results
Safety Analysis Set

Listing 16.4.4.5
Other Laboratory Test Results
Safety Analysis Set

Listing 16.4.5
Vital Signs Results
Safety Analysis Set

Actual Treatment	Subject ID	Visit (Study Day)	Date	Scheduled Time	Weight (kg)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	Body Temperature (°C)	BMI (kg/m^2)
xxxxxxx	xxx-xxxxx	2 (1)	DDMMMYYYY	Pre-dose	xx.x	Xxx	xx	xx	xx.x	xx
				x	xx.x	Xxx	xx	xx*	xx.x	xx
				xx	xx.x	Xxx	xx	xx	xx.x	xx
				xx	xx.x	Xxx	xx	xx	xx.x	xx
				xx	xx.x	Xxx	xx	xx	xx.x	xx
		3 (4)	DDMMMYYYY							
		U (25)								

Footnote: Clinically significant findings are signified by a *. U = unscheduled visit.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.4.6
Brief Physical Examination
Safety Analysis Set

Actual Treatment	Subject ID	Physical Examination Performed?	Body System	Results	Comments
xxxxx	xxx-xxxxxx	Done	Thorax/Lungs	Normal	
			Cardiovascular System	Abnormal CS	xxxx
			Neurological Examination	Not Examined	xxxx
xxxxx	xxx-xxxxxx	Not Done			

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY

Listing 16.4.7
Electrocardiogram (ECG) Results
Safety Analysis Set

Actual Treatment	Subject ID	Visit (Study Day)	Date/Time of Assessment	Heart Rate (Bpm)	PR Interval (ms)	RR Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTcF Interval (ms)	Finding
xxxxxxx	xxx-xxxxx	2 (1)	DDMMYYYY/ HH:MM	xxx	xxx	xxx	xxx	xxx	xxx	Normal
		xxx		xxx	xxx	xxx	xxx	xxx	xxx	Abnormal, NCS
		xxx		xxx	xxx	xxx	xxx	xxx	xxx	
		xxx		xxx	xxx	xxx	xxx	xxx	xxx	
		U (25)		xxx	xxx	xxx	xxx	xxx	xxx	

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas. U= unscheduled visit.
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming notes: Triplicate measures will be recorded in the visit description. I.e. 2 (1) – triplicate 1, 2 (1) – triplicate 2 etc.

Listing 16.4.8
Individual GBR830 Serum Concentration (ng/mL) Data
Pharmacokinetic Analysis Set

LLOQ=xx.xx ng/mL

Subject ID	Study Day	Time Point (h)		Date	Time	Time Deviation (mins)	Reported Concentration (ng/mL)	Comment
		Scheduled	Actual					
xxx-xxxxxx							xxx.x	
							xxx.x	
							xxx.x	
							xxx.x	
							xxx.x	
							xxx.x	
					…		xxx.x	
xxx-xxxxxx								
					Etc.			

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Programming note: repeat for all time points and dose 2 – see SAP text for dose interval details.

Listing 14.4.9

Individual Pharmacokinetic Parameters of GBR830
Pharmacokinetic Analysis Set

Subject ID	Dose Interval	AUC0-t (µg.h/mL)	AUC0-tau (µg.h/mL)	AUC∞ (µg.h/mL)	Cmax (µg/mL)	Tmax (h)	λz (1/h)	t1/2 (h)	Vd (L)	CL (L/h)
xx-xxxxxx	Dose 1	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	NA	NA	xxx.x	xxx.x
	Dose 2	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
xx-xxxxxx	Dose 1	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	NA	NA	xxx.x	xxx.x
	Dose 2	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
xx-xxxxxx	Dose 1	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	NA	NA	xxx.x	xxx.x
…. Etc.										

Footnote: AUC0-∞=area under the (serum) concentration-time curve to infinity; AUC0-t=area under the (serum) concentration-time curve to the last time point where quantifiable concentration is observed; AUC0-tau=area under the (serum) concentration-time curve to the last observed time point in the interval; CL=clearance; Cmax=maximum concentration; Tmax=Time of Cmax. t1/2=terminal half-life; Vd=volume of distribution.

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Listing 16.4.10
Time Points used to Calculate the GBR830 Elimination Rate Constant (λz)
Pharmacokinetic Analysis Set

Subject ID	Lower Time (h)	Upper Time (h)	Number of Points	Adjusted R-Square	λz (1/h)	t½ (h)
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx
xx-xxxxxx	xxx	xxx	xx	x.xxxx	xx.xxxx	xxx

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

Listing 16.4.11
Reasons Pharmacokinetic Parameters Could Not be Determined
Pharmacokinetic Analysis Set

Subject ID	Pharmacokinetic Parameter (Unit)	Original Value	Comment
xx-xxxxxx	xxxxxxx (xx)	xxx.x	xxxxxxxxxxxxxxxxxxxxxx
	xxxxxxx (xx)	xxx.x	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxxx (xx)	xxx.x	xxxxxxxxxxxxxxxx
xx-xxxxxx	xxxxxxx (xx)	xxx.x	xxxxxxxxxxxxxxxxxxxxxxxxxx

Listing 16.5.2
Protocol Deviations
Randomized Subjects

Planned Treatment	Subject	Protocol Deviation Number	Date reported (Visit)	Deviation coding	Deviation Description, verbatim	Description of the actions taken	Reported to Ethics?
xxxxxxxxxx	xx-xxxxxx	xx	DDMMMYYYY (x)	Subject non-compliance with study procedures	xxx	List the description of the actions taken	Yes
		xx	DDMMMYYYY (x)	Randomization error	xxx	List the description of the actions taken	No

SOURCE: X:\Numerus\Studies\XXX\XXXYYY\Analysis\Prod\Progs\XXXXX.sas
Date/time of run: DDMMMYYYY HH:MM; Date of data extraction: DDMMYYYY
Analysis Plan: 06Jul2017 Confidential Page X of Y

12. REFERENCES

1. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine. 17 (6): 863–71.Basra et al. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008; 159: 997-1035.
2. Finlay et al. A simple practical measure for routine clinical use. Clin Exp Dermatol.1994;19:210-16
3. Hanifin et al. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;92:44-7.
4. Hanifin et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol, 2001, 10: 11-18.
5. Kunz B et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European task for on atopic dermatitis. Dermatology. 1997:195:10-19.
6. No authors listed. (1993). Severity scoring of atopic dermatitis: the SCORAD index. Dermatology, 1993, 186: 23-31.